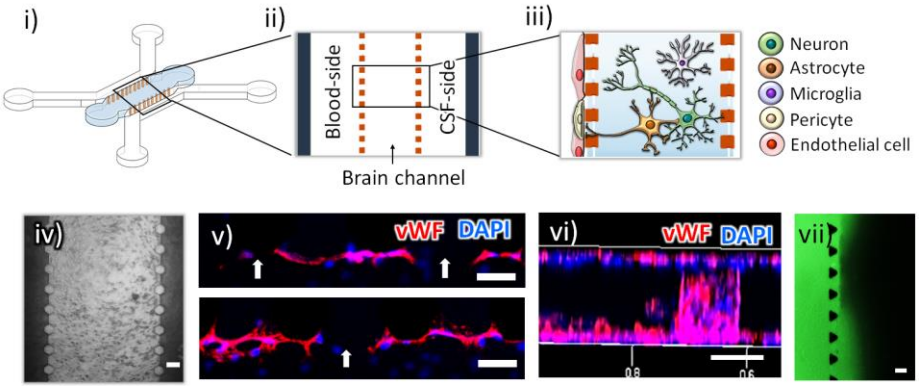
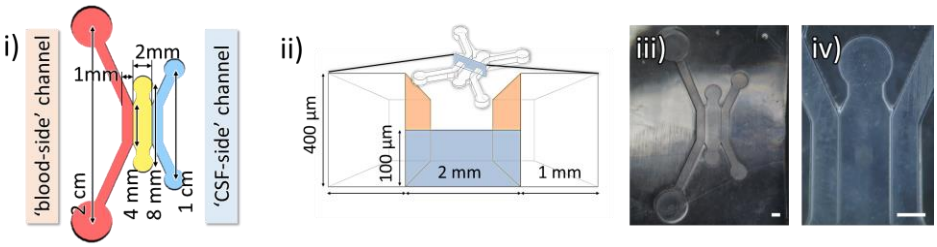
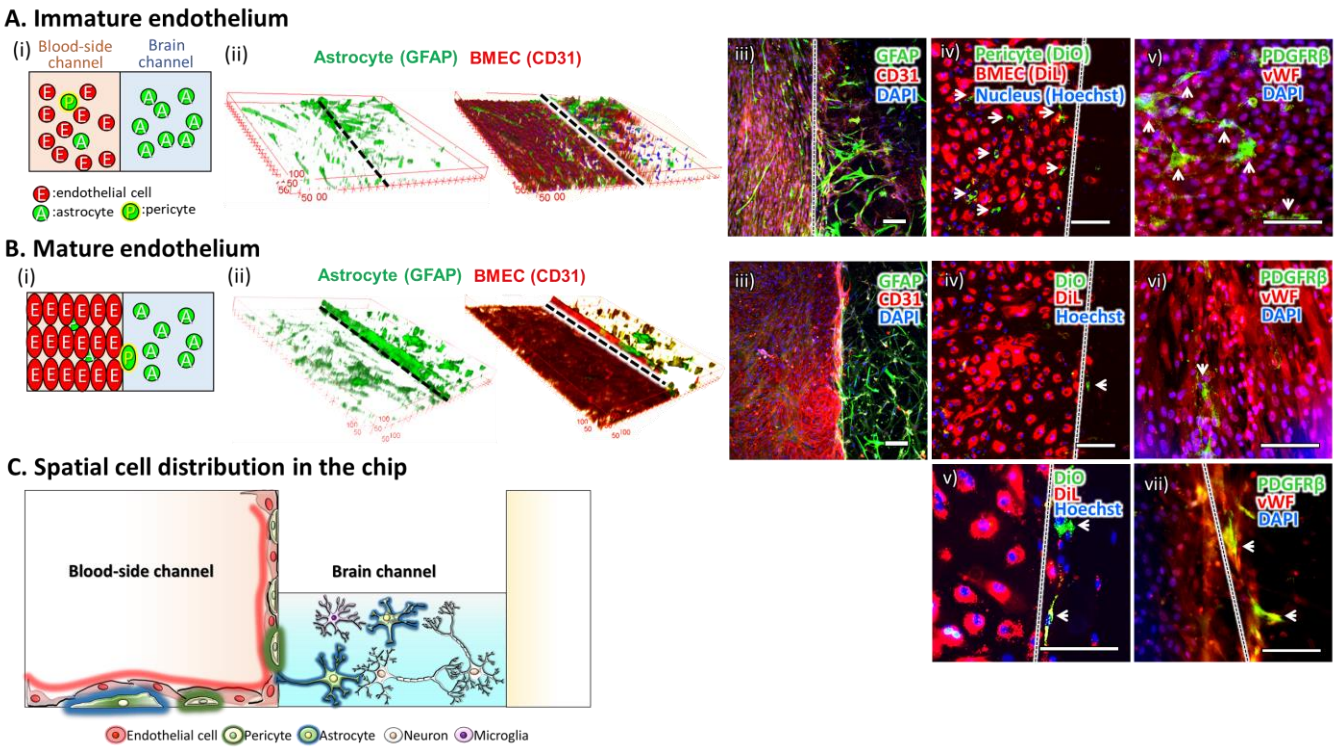
TABLE OF CONTENTS



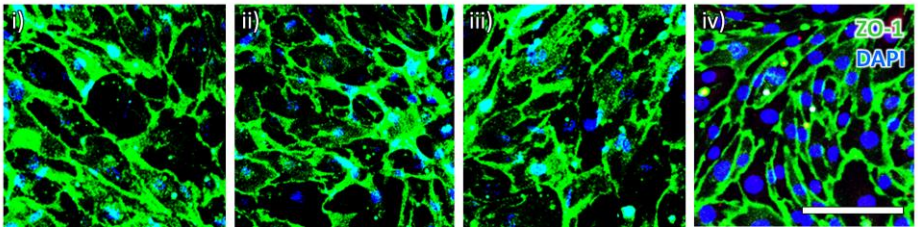
Supplementary Fig. **1 | Endothelium defects in a chip with micro-poles. (i-iii)** Chip design with micro-poles. The schematic illustration of the chip design w/ micro-poles (i-ii) and the spatial distribution of the NVU constituent cells in the chip (iii). **(iv)** A phase contrast image showing the hydrogel deployed in the middle 'brain' channel. **(v-vi)** Single layers (v) and a reconstructed side view (vi) of confocal microscopic images showing the endothelium (immunostained as red by vWF, a marker of endothelial cells) on the side wall of the hydrogel in the 'brain' channel. The white arrows indicate the defects on the endothelium. **(vii)** The green fluorescence probes (FITC-dextran, 4k Da) injected in the 'blood-side' channel diffused unevenly across the endothelium formed in the chip w/ micro-poles. The image was taken one hour after adding the probes. Scale bars: 100 μm.



Supplementary Fig. 2 | A chip design without micro-poles. (i-ii) The dimensions of a microfluidic chip. **(iii)** The image of a master mold prepared by a 3D printer. **(iv)** The image of a PDMS replica. Scale bars: 1 mm.



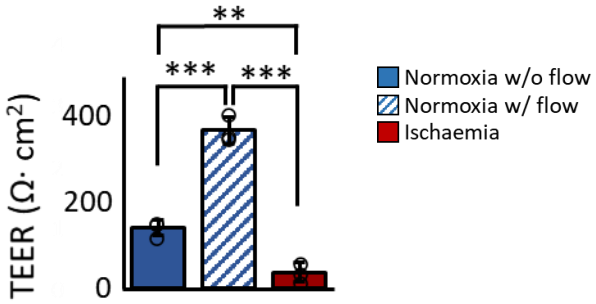
Supplementary Fig. 3 | Spatial cell distribution in our chip. A. Immature endothelium. (i) A schematic diagram of the top view of the cell distribution. **(ii - iii)** Astrocytes (immuno-stained as green by GFAP) are exposed among BMEC (immuno-stained as red by CD31) and clearly visible. **(iv)** Pericytes (pre-stained as green by DiO) show similar pattern and are clearly visible among the endothelial cells (pre-stained as red with DiL). White arrows indicate the pericytes. **(v)** Pericytes and BMEC were immuno-stained by a pericyte marker, PDGFRβ, and an endothelial cell marker, vWF, respectively. **B. Mature endothelium. (i)** A schematic diagram of the top view of the cell distribution. **(ii - iii)** Astrocytes (immuno-stained as green by GFAP) are covered by the mature endothelium (immuno-stained as red by CD31) and are barely visible. **(iv-v)** Pericytes (pre-stained as green by DiO) show similar pattern and are covered underneath the mature endothelium (pre-stained as red with DiL). **(vi-vii)** Pericytes and BMEC were immuno-stained by PDGFRβ and vWF, respectively. Only a few pericytes are exposed among the BMEC and on the side-wall of the 'brain' channel. Dashed lines are the hydrogel boundaries. White arrows indicate pericytes. **C. A schematic diagram of the final cell distribution.** A cross-sectional view. Scale bars: 100 μm.



Supplementary Fig. 4 | Morphological changes of hBMEC due to the interaction with glial cells. Fluorescent images showing the morphology of hBMEC when they were cultured alone **(i)**, co-cultured with pericytes **(ii)**, astrocytes **(iii)**, or both pericytes and astrocytes **(iv)**. Normal morphology of hBMECs was observed only when both pericytes and astrocytes were co-cultured. hBMECs were immunostained with ZO-1 and cell nuclei were stained with DAPI. Scale bars: 200 μm.

BMEC	+	+	+	+	+
Astrocyte	–	+	–	+	+
Pericyte	–	–	+	+	+
Flow	–	–	–	–	+
P_{app} (cm/s) for FTIC-dextran 4k Da	$1.9X10^{-5}$ ± $8.9X10^{-6}$	$6.6X10^{-6}$ ± $2.8X10^{-6}$	$8.9X10^{-6}$ ± $5.4X10^{-6}$	$2.5X10^{-6}$ ± $7.8X10^{-7}$	$5.8X10^{-7}$ ± $1.8X10^{-7}$
P_{app} (cm/s) for FTIC-dextran 70k Da	$1.8X10^{-6}$ ± $4.2X10^{-7}$	$1.5X10^{-6}$ ± $3.7X10^{-7}$	$1.5X10^{-6}$ ± $3.1X10^{-7}$	$4.2X10^{-7}$ ± $2.5X10^{-7}$	$7.8X10^{-8}$ ± $3.8X10^{-8}$

Supplementary Table 1 | Apparent permeability coefficients, P_{app}, of the endothelium with different cell compositions in the chip (actual values of P_{app} shown in logarithmic scale in **Fig. 1a. x**). The data are presented as mean ± s.d. (n=5).



Supplementary Fig. 5 | TEER values of the BBB. The TEER value of BBB significantly increases in the presence of flow compared to the cells in a static culture (n=3). Statistical analysis was performed using one-way ANOVA with Bonferroni-Holm post hoc test (p<0.001 between w/o and w/ flow in normoxic samples, p<0.001 between normoxic samples w/ flow and ischaemic samples, and p=0.0038 between normoxic samples w/o flow and ischaemic samples). 'n' denotes the number of biological replicates, independent chips, used in each experimental condition. The error bars on the bar graph show s.d. from the mean. Dots along the bar graphs represent individual data points. Statistical significance is denoted as '**', or '***' for p<0.01, or p<0.001, respectively.

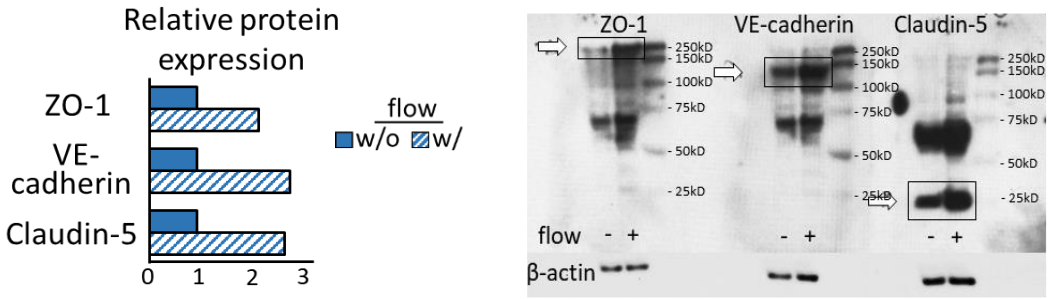
Method for TEER measurement

To quantitatively evaluate the tightness of the formed endothelium, we adopted an approach measuring the trans-endothelial electrical resistance (TEER), as in a previous work listed below (1). Briefly, we inserted two chloridized silver electrodes (0.5 mm diameter, Surepure Chemetals) into two side channels, one for each channel, spanning across the entire BBB, and measured the electrical resistance using a DC resistance meter with a measurement range of 400 Ω - 40 MΩ (EXTECH, model: MN36) that automatically adjusted to the best range. The TEER across the endothelium was calculated according to the equation below:

$$\mathrm{TEER} = \mathrm{R} \cdot \mathrm{A}$$

, where R = electrical resistance (Ω) and A = area of the endothelium (cm^2). As the measurement time increased, the resistance value tended to decrease with fluctuation. The TEER value of each sample thus was determined as the value first recorded stably for two seconds or longer. All TEER data were presented after baseline adjustment, i.e. subtracting the baseline value of the control samples (hydrogel only in the 'brain' channel).

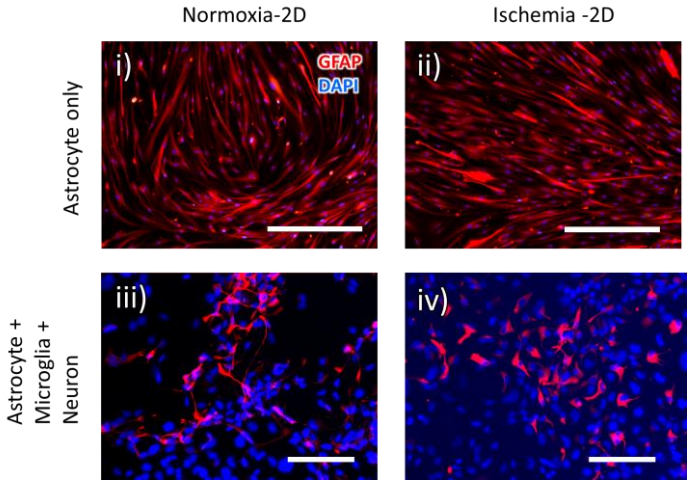
(1) Mathiu, O., ávan der Meer, A. D., JungáKim, H., ávan der Helm, M. W. & den Berg, A. Measuring direct current trans-epithelial electrical resistance in organ-on-a-chip microsystems. *Lab on a Chip* **15**, 745-752 (2015).



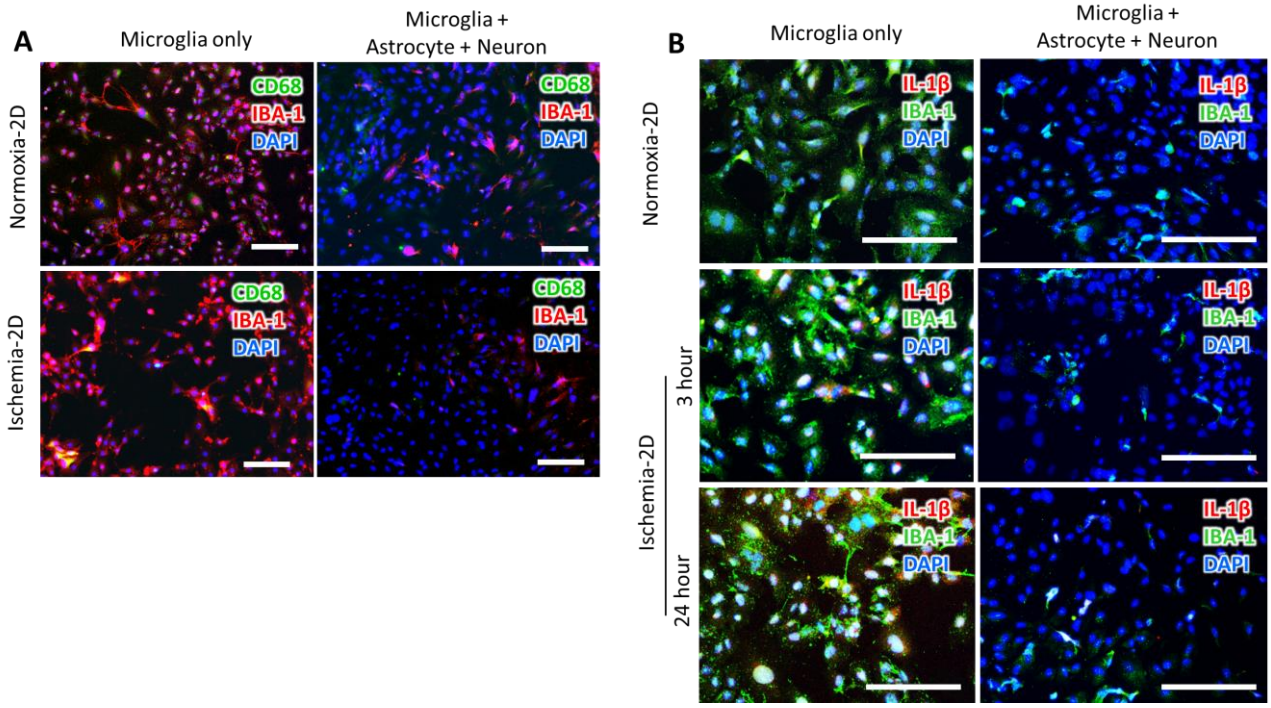
Supplementary Figure 6 | Expression changes of BBB markers by flow. Western blots showing the expression levels of the BBB markers, ZO-1, VE-cadherin, and Claudin-5. The expression levels were measured with the cell lysates of four independent chips at each condition.

Method for Western blot analysis

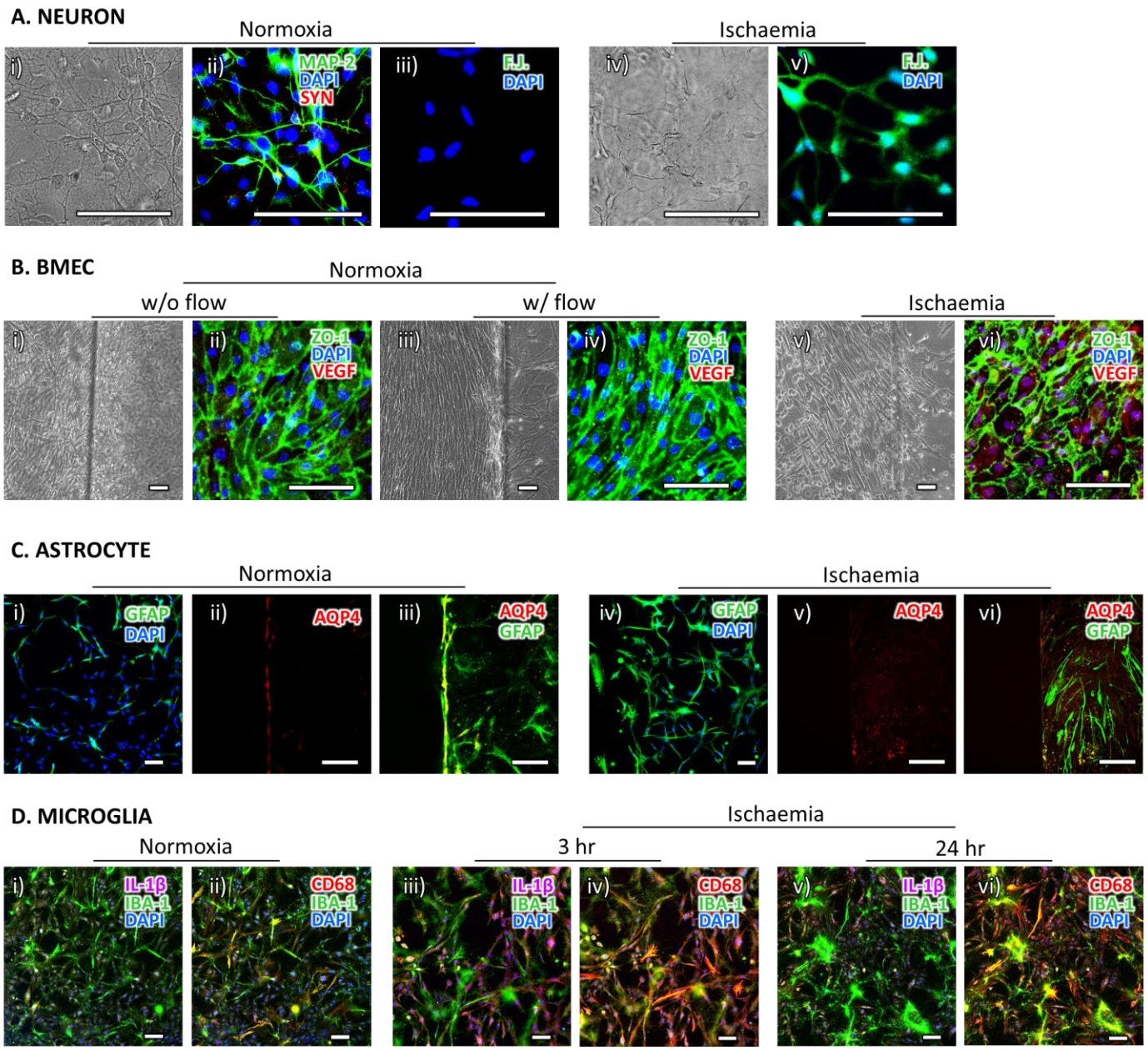
To analyze the protein expression level with western blotting, 20 μL of lysis buffer (radio-immunoprecipitation assay (RIPA) buffer (Sigma Aldrich Cat. No.: R0278) + 0.5 mM EDTA + 1× Halt protease and phosphatase inhibitor cocktail (Thermo Fisher, Cat. No.: 78430)) was added to the 'blood-side' channel of the chip and the cell lysates were harvested by thorough pipetting. After collecting supernatants by centrifugation at 14,000 rpm for 15 min at 4 °C, we determined the protein concentration with the BCA protein assay kit (Thermo Fisher Cat. No.: 23225) using bovine serum albumin (BSA) as standards. Total protein was loaded onto 10% polyacrylamide gels and separated proteins were transferred to a PVDF membrane (Thermo Fisher, LC2002). The membrane was blocked for 1 hour in 1×TBST (Tris buffered saline + 0.1% Tween 20) with 5% BSA and then incubated with primary antibodies overnight at 4 °C followed by three washes with 1×TBST. Protein expression was detected using specific primary antibodies against Claudin-5 (Invitrogen, Cat. No.: 34-1600, 1:150), VE-cadherin (Invitrogen, Cat. No.: 14-1449-82, 1:200), ZO-1 (Invitrogen, Cat. No.: 339100, 1:250), and β-actin (Sigma, Cat. No.: A1978, 1:20,000). After incubation with secondary antibodies at room temperature for 1-3 h, the blots were washed three times with 1×TBST and developed with WesternBright ECL HRP substrate (Advansta, Cat. No.: K12045-D50). The level of protein expression was analyzed by densitometry using ImageJ (NIH) and normalized to each corresponding β-actin expression.



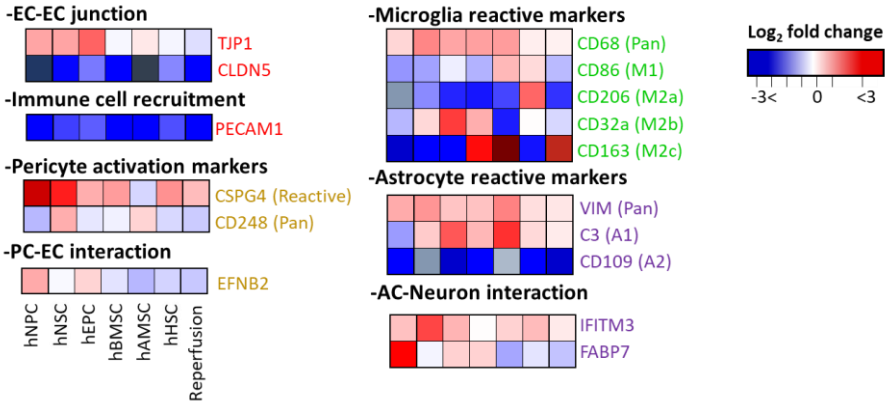
Supplementary Fig. 7 | Astrocyte behaviors in traditional 2D cultures. The expression of an astrocyte marker, Glial Fibrillary Acidic Protein (GFAP), in the astrocytes cultured in traditional 2D culture plates. The astrocytes were cultured alone (i & ii) or co-cultured with microglia and neurons (iii & iv) under normoxia (i & iii) or ischaemia (ii & iv) conditions. Scale bars: 200 μm.



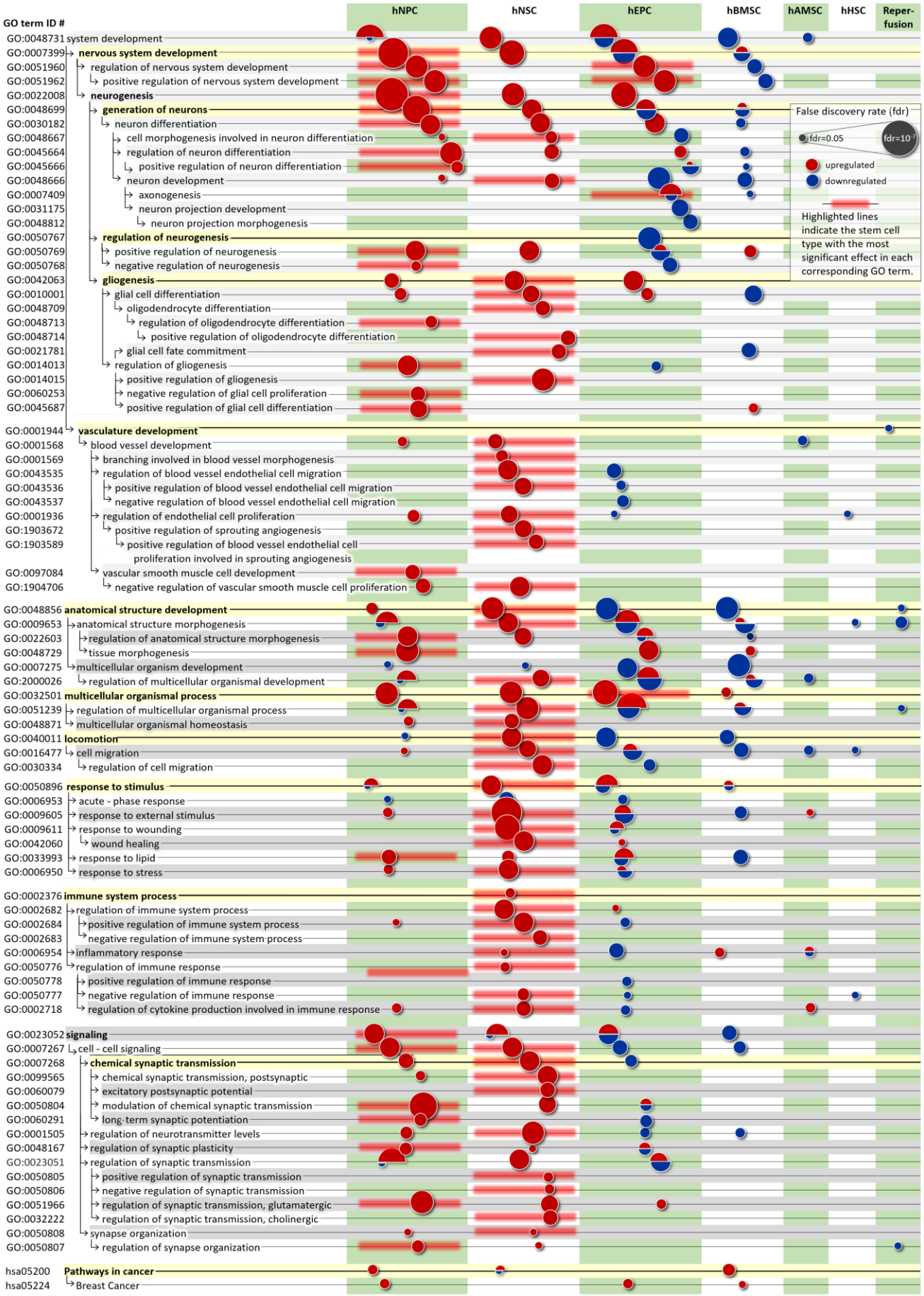
Supplementary Fig. 8 | Microglia behaviors in traditional 2D cultures. Microglia were immunostained by its specific marker, IBA-1, and inflammatory microglia markers, CD68 **(A)** or IL-1β **(B)**. Scale bars: 200 μm.



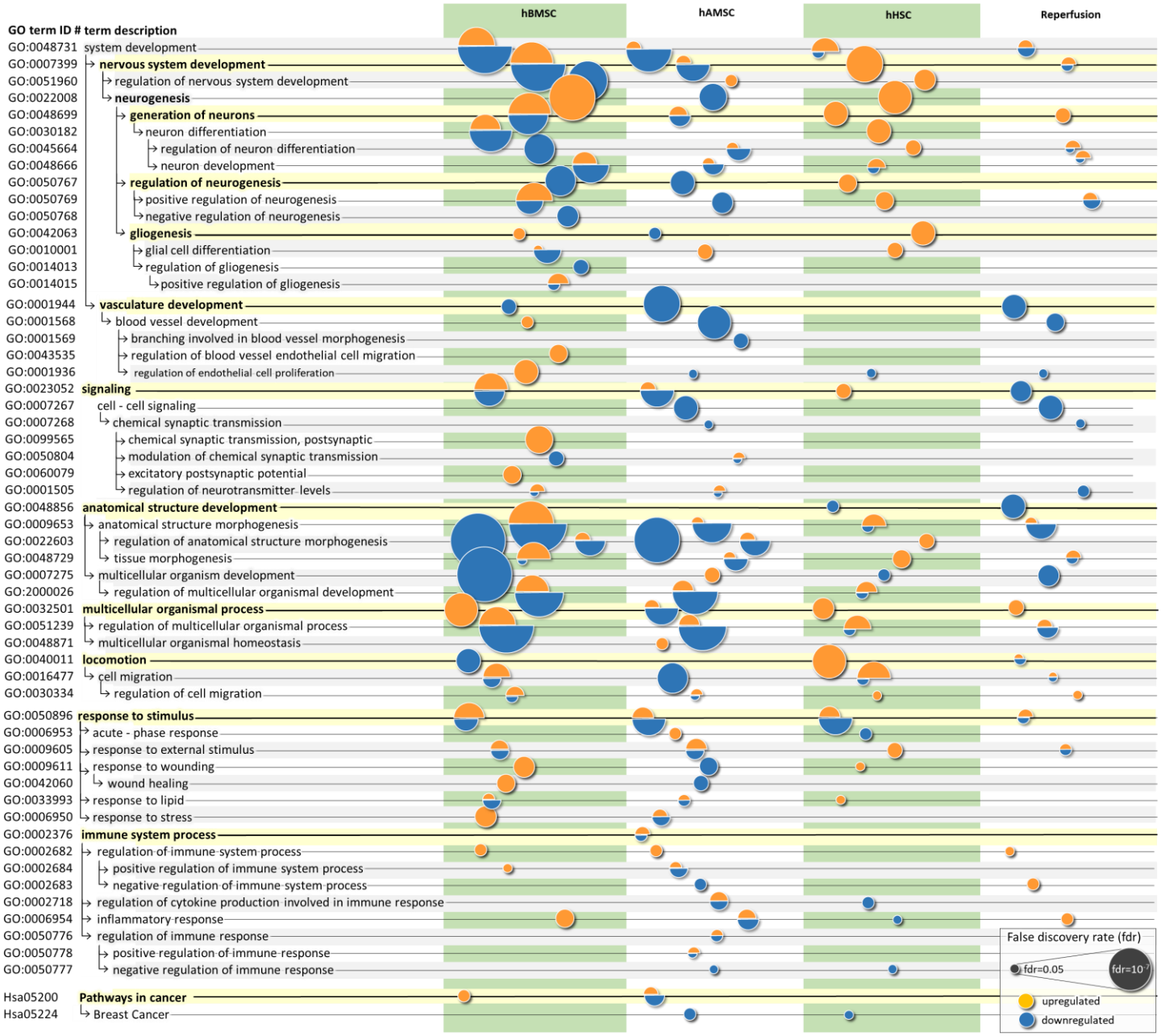
Supplementary Fig. 9 | Additional images of the NVU cells in the chip. A. Neurons in normoxic (i-iii) and ischaemic samples (iv-vi). (i & iv) Phase contrast images. (ii) A fluorescent image of mature neuronal markers, MAP-2 and Synapsin I and II (SYN). (iii & v) Fluorescent images of Fluoro-Jade C (F.J.), a neuronal degeneration marker. **B. BMEC** in normoxic samples without (i & ii) or with flow (iii &iv), or in ischaemic samples (v & vi). (i, iii & v) Phase contrast images. (ii, iv & vi) Fluorescent images of ZO-1, a BBB marker, and VEGF, an angiogenic factor. **C. Astrocytes** in normoxic (i-iii) and ischaemic samples (iv-vi). Fluorescent images of AQP4, a water channel protein (ii & v), and images of GFAP, an astrocyte marker (i & iv), are merged together in iii & vi, respectively. **D. Microglia** in normoxic samples (i & ii) and in samples with ischaemia for 3 hours (iii & iv) and 24 hours (v & vi). IBA-1 is a microglia marker. IL-1β and CD68 are microglial inflammatory markers. Scale bars: 100 μm.



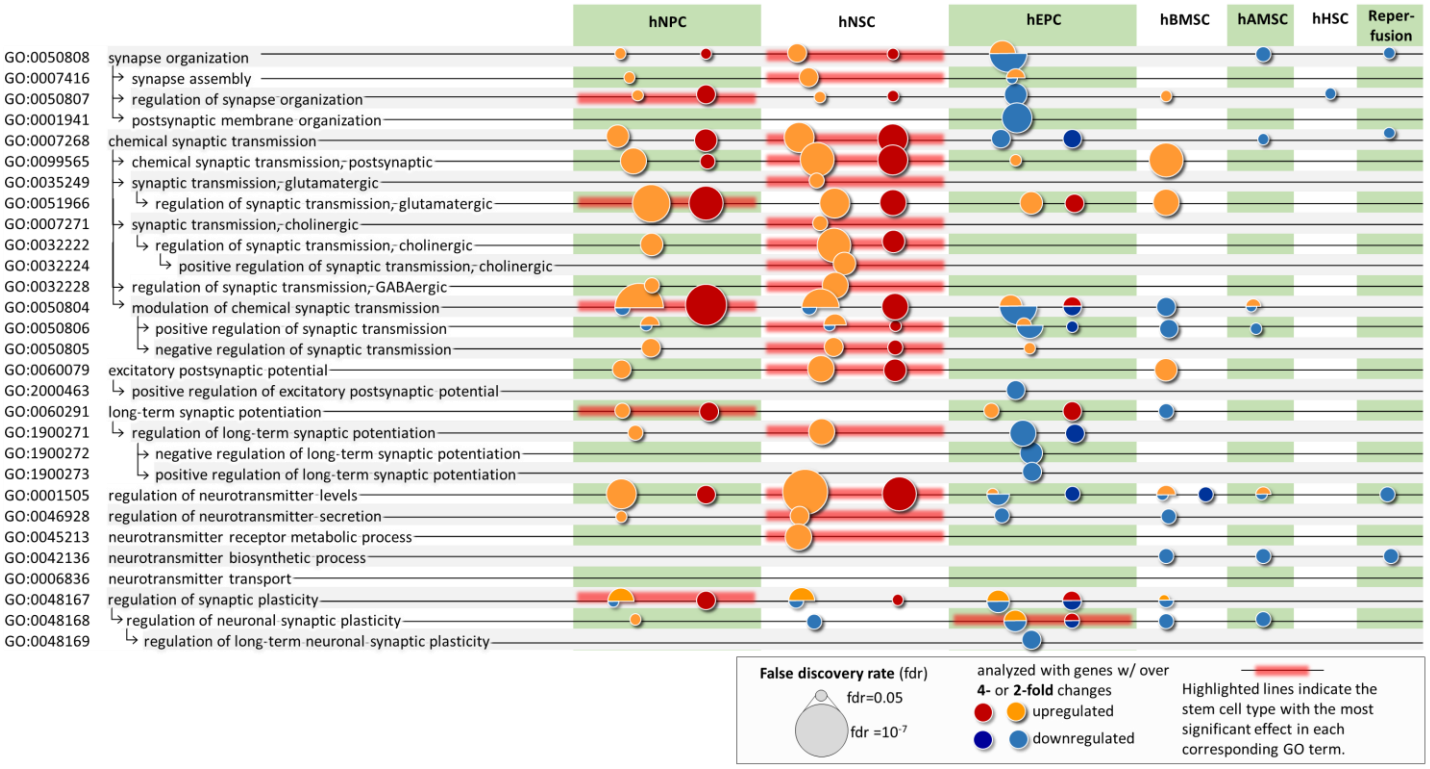
Supplementary Fig. 10 | Gene expression alteration of glia phenotype markers by therapeutic stem cells and reperfusion. Magnified heatmap of Figure 5a i. The gene lists colored in red, yellow, green, and purple are the phenotype markers of endothelial cells, pericytes, microglia, and astrocytes, respectively.



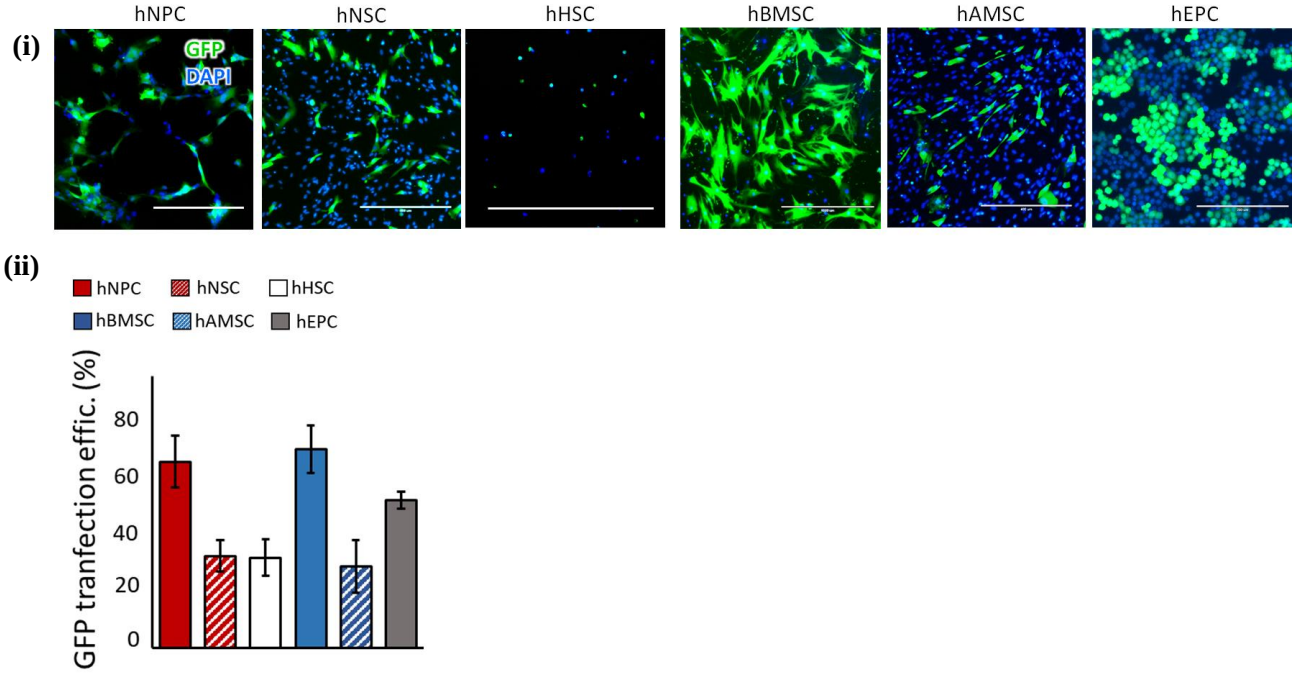
Supplementary Fig. 11 | GO terms from the functional enrichment analysis on the genes with over 4-fold expression changes.



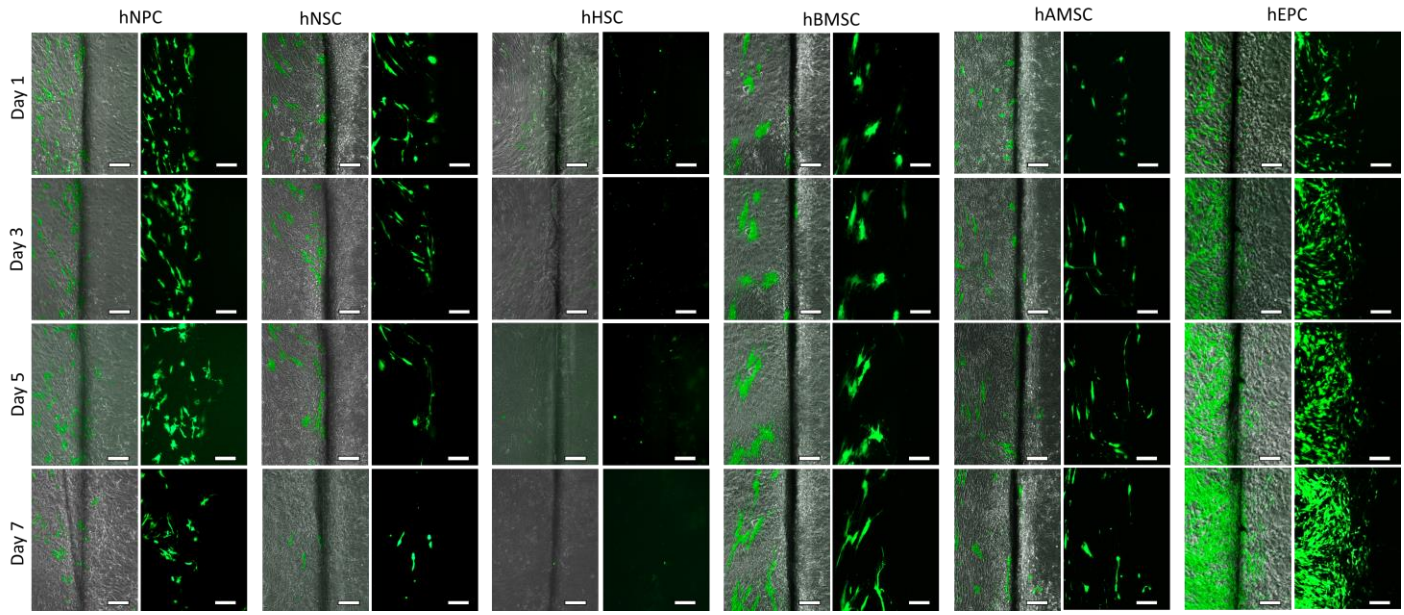
Supplementary Fig. 12 | GO terms from the functional enrichment analysis on the genes with over 2-fold expression changes.



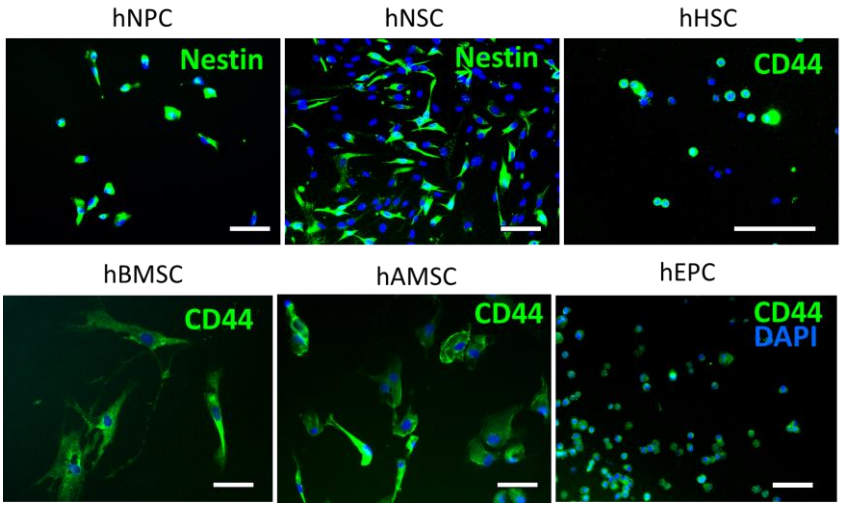
Supplementary Fig. 13 | GO terms related to synapse and neurotransmitters, from the functional enrichment analysis on the genes with over 4- and 2-fold expression changes. The lines highlighted in red indicate the stem cell type most influential for each GO term.



Supplementary Fig. 14 | GFP transfection efficiency of each stem cell type. (i) Images of the Green Fluorescent Protein (GFP)-expressing stem cells taken 3 days after adding GFP Lentiviral Vectors. Scale bars: 400 μm. **(ii)** GFP transfection efficiency was calculated by taking the ratio of the number of GFP-expressing cells over the overall cell number.



Supplementary Figure 15 | Time-lapse images of GFP-expressing stem cells invading across the BBB on a chip. Left-side panels in each stem cell type show the merged images of a phase contrast image and a fluorescent image. Right-side panels show the fluorescent images alone. Scale bars: 200 μm



Supplementary Figure 16 | Fluorescent images showing the expression of stem cell markers in 2D culture before the transplantation. Scale bars: 100 μm

Supplementary Table 2 | Functional characteristics and relevant references of the genes in **Figure 2**, **3**, and **4**.

Apoptosis		RIPK2	Receptor interacting serine/threonine kinase 2	- Encodes a potent activator of NF-Kb and inducer of apoptosis. - The expression of RIPK2 is significantly elevated after ischaemic stroke [1].
		PSMB8	Proteasome subunit beta 8	- Encodes β5i which often functions as a subunit of the immunoproteasome. PSMB8 promotes the proliferation and migration and induces apoptosis of glioma cells [2]. - PSMB8 expression is induced by ischaemic stroke. It increases infarction volume and promotes inflammatory reaction [3].
		HSPB1	Heat shock protein family B (small) member 1	- HSPB1 is strongly induced during the stress response such as ischaemia. It has powerful neuroprotective effects, increasing the survival of cells subjected to cytotoxic stimuli [4].
		GADD45B	Growth arrest and DNA damage inducible beta	- This gene is an important factor in DNA repair, apoptosis, cell survival, and growth arrest. - GADD45B expression is significantly increased in ischaemic brain [5]. Knockout of GADD45B significantly increases neuronal apoptosis [6].
		MCL1	MCL1 apoptosis regulator, BCL2 family member	- Encodes an anti-apoptotic protein, which is a member of the Bcl-2 family. - The expression of MCL1 increases as early as 4 hours after middle cerebral artery occlusion (MCAO), peaks at 24 hours, and then declines, but still remains high, at 72 hours in rats model [7].
		XIAP	X-linked inhibitor of apoptosis	- Encodes a protein that belongs to a family of apoptotic suppressor proteins. - XIAP expression increases after focal cerebral ischaemia [8].
Redox		HMOX1	Heme oxygenase 1	- Heme oxygenase is an essential antioxidant enzyme in heme catabolism and it acts as stress defense. - Ischaemic stroke strongly upregulates HMOX1 expression [9].
		TXNIP	Thioredoxin interacting protein	- Encodes a thioredoxin-binding protein that is a member of the alpha arresting protein family. Thioredoxin (Trx) is a thiol-oxidoreductase that is a major regulator of cellular redox signaling which protects cells from oxidative stress. - Cerebral ischaemia strongly increases TXNIP expression. TXNIP activation is a key event linking oxidative stress to inflammation and apoptosis in neurons [10].
		TXNRD1	Thioredoxin reductase 1	- This gene belongs to the pyridine nucleotide-disulfide oxidoreductase family, and is a member of the thioredoxin (Trx) system. It is important in detoxifying quinones and maintaining the cellular redox balance. - The expression of TXNRD1 increases following ischaemic stroke [11].
		SOD2	Superoxide dismutase 2	- This gene is a member of the iron/manganese superoxide dismutase family. It encodes an enzyme that efficiently converts superoxide to the less reactive hydrogen peroxide. - Ischaemia induces the expression of SOD2. SOD2-deficient mice present higher levels of oxidative stress after ischaemic stroke [12].

Trophic factors		IGFR2 (FCGR2A)	Fc fragment of IgG receptor IIa	- Encodes one member of a family of immunoglobulin Fc receptor genes found on the surface of many immune response cells. FC receptors induce powerful responses that activate, regulate, and modulate immunity [13] . - FCGR2A expression increases during inflammatory processes [14] and causes apoptosis [15].
		IGFR1 (FCGR1A)	Fc fragment of IgG receptor Ia	- Encodes a protein that plays an important role in the immune response. - FCGR2A expression increases in activated microglia during neuro-inflammatory processes [16].
		IGF1	Insulin like growth factor 1	- Encodes a protein that is similar to insulin in function and structure. It possesses both neurotrophic and angiogenic properties [17]. - IGF-1 is widely considered neuroprotective in brain injury and stroke. Decreased IGF-1 levels are linked to increased risk and worse functional outcome after ischaemic stroke [18].
		VEGFA	Vascular endothelial growth factor A	- This gene is a member of the PDGF/VEGF growth factor family. It induces angiogenesis [19] and exerts direct trophic and protective effects on neurons [20]. - VEGFA expression increases following ischaemic stroke [21].
		VEGFR2 (KDR)	kinase insert domain receptor	- Most of the VEGF bio-functions are mediated by interacting with VEGFR2. Angiogenesis and neurogenesis are dependent on the VEGF/BEGFR2 signaling. - VEGFA expression increases following ischaemic stroke. It plays a role in post-stroke angiogenesis and neurogenesis [10].
		VEGFC	Vascular endothelial growth factor C	- Encodes a member of the platelet-derived growth factor/vascular endothelial growth factor (PDGF/VEGF) family. It has potent angiogenic effects in vivo [22]. - VEGFC expression transiently increases after focal cerebral ischaemia [23].
		FGFR3	Fibroblast growth factor receptor 3	- Encodes a member of the fibroblast growth factor receptor (FGFR) family. - FGFR3 is the receptor of FGF2. FGF2 and FGFR3 play an important role in the angiogenic process [24].
		FGF2	Fibroblast growth factor 2	- Encoded a member of the fibroblast growth factor (FGF) family. FGF2 and FGFR3 play an important role in the angiogenic process [24]. - Ischaemic stroke induces FGF2 expression. [25]
		TGFB1	Transforming growth factor beta 1	- Encodes a secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins. It is an anti-inflammatory cytokine with neuroprotective activity against ischaemia-induced neuronal death [26]. - TGFB1 is required to elicit proper CNS angiogenesis [27]. - TGFB1 expression increases in human brain tissue and cerebrospinal fluid after ischaemia [28].
		TGFB3	Transforming growth factor beta 3	- Encodes a secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins. It is a multifunctional cytokine involved in development, immune function and cell cycle control. It is a potent survival factor for midbrain dopaminergic neuron [29].

				- TGFB3 is required to elicit proper CNS angiogenesis [27]. - TGFB3 is activated after ischaemic stroke [30].
		RELN	Reelin	- Encodes a protein involved in migration of newborn neurons during development. Reelin deficiency impairs neurogenesis and exacerbates ischaemic neuronal injury in the adult brain of mice [31].
		RET	Ret proto-oncogene	- Encodes a transmembrane receptor and member of the tyrosine protein kinase family of proteins. It is a component of the glial cell line-derived neurotrophic factor (GDNF) receptor complex which has potent dopaminergic neurotrophic properties [32]. - The expression RET is increased by ischaemic stroke [33].
		HBEGF	Heparin binding EGF like growth factor	- Encodes a member of the EGF family. It is induced by cerebral ischaemia [34] and contributes to functional recovery after ischaemic stroke by promoting neurogenesis and angiogenesis [35].
		ADM	Adrenomedullin	- Encodes a potent vasodilatory peptide which induces angiogenesis after ischaemia [36]. It also exerts antiapoptotic effects on a variety of cells [37]. - Adrenomedullin infusion reduces apoptotic cells in both neurons and glial cells in the ischaemia area of the brain [38].
		ANGPT2	Angiopoietin 2	- Encodes a protein that is an antagonist of angiopoietin 1 (ANGPT1) and endothelial TEK tyrosine kinase (TIE-2, TEK). It is an angiogenic regulator. - The expression of ANGPT2 increases after stroke in adults after stroke [39].
		BDNF	Brain derived neurotrophic factor	- Encodes a member of the nerve growth factor family of proteins which exerts neuroprotective, neuroplastic, neurogenic, and angiogenic effects thus leading to recovery after CNS insults [40]. - The expression of BDNF increases after stroke which promotes angiogenesis, synaptogenesis, and functional recovery [41].
		SULF1	Sulfatase 1	- Encodes an extracellular heparan sulfate endosulfatase that modulates heparan sulfate proteoglycans (HSPGs) during cerebellar development, thereby regulating neuronal survival and neurite outgrowth. It has neuroprotective and neurite outgrowth promoting functions [42].
		ECSCR	Endothelial cell surface expressed chemotaxis and apoptosis regulator	- Encodes a protein that enhances the sensitivity and responsiveness of VEGF receptors towards VEGF stimulation and thus modulates angiogenesis [43]. - Expression of ECSCR is increased by inflammatory processes [44].
		BMP2	Bone morphogenetic protein 2	- Encodes a secreted ligand of the TGF-beta superfamily of proteins that binds to TGF-beta receptors. BMP2 signaling pathway modulates angiogenesis [45]. - BMP plays important roles in cell specification, neuronal migration, survival, and dendritic development. BMP-2/4 expression decreases in ischaemic astrocytes in vitro. It inhibits both neurogenesis and oligodendrogenesis [46].

		DLK1	Delta like non-canonical Notch ligand 1	- Encodes a transmembrane protein that contains multiple epidermal growth factor repeats. - DLK1 activates p38 MAPK which plays a central role in inflammation, as well as cell proliferation, apoptosis, environmental stress, and neuropathic pain [47].
Pro-inflammatory cytokines		IL1B	Interleukin 1 beta	- Encodes a protein that is a member of the interleukin 1 cytokine family. -Cytokines are a group of small glycoproteins that are produced in response to an antigen and act as mediators for regulating the innate and adaptive immune systems. Cytokines are upregulated in the brain in a variety of diseases including stroke [48]. - M1 Microglia release IL1B in ischaemic stroke [49].
		LGALS3	Galectin 3	- Encodes a member of the galectin family of carbohydrate binding proteins. - Galectin 3 has been increasingly used as a marker of microglia activation. Its expression is upregulated in activated microglia after ischaemic stroke [50].
		IL32	Interleukin 32	- Encodes a member of the cytokine family that induces the production of other cytokines such as TNF-alpha, IL-1β, IL-6, and IL-10 and thereby plays an important role in inflammatory diseases [51].
		SPHK1	Sphingosine kinase 1	- Catalyzes the phosphorylation of sphingosine to form sphingosine-1-phosphate (S1P). SPHK and S1P activate signaling molecules implicated in the induction of cerebral ischaemic tolerance [52]. - SPHK1 is upregulated in the ischaemic brain [53].
		IL8RB (CXCR2)	C-X-C motif chemokine receptor 2	- Encodes a protein that is a receptor for interleukin 8 (IL8). This receptor also binds to chemokine (C-X-C motif) ligand 1. - Its expression is increased after ischaemic stroke [54].
		IFNG	Interferon gamma	- Encodes a soluble cytokine that is a member of the type II interferon class. The encoded protein is secreted by cells of both the innate and adaptive immune systems. - Interferon gamma is a pro-inflammatory cytokine. Its level increases after ischaemic stroke which enhances neural injury [55].
		PTX3	Pentraxin 3	- Encodes a member of the pentraxin superfamily and the expression of this protein is induced by cytokines in response to inflammatory stimuli. - PTX3 expression is induced by proinflammatory signals after ischaemic brain injury. The absence of PTX3 strongly compromises blood-brain barrier integrity and resolution of brain edema during recovery after ischaemic injury [56].
		IL12A	Interleukin 12A	- Encodes a subunit (alpha) of a cytokine that is required for the T-cell-independent induction of interferon (IFN)-gamma [57], a pro-inflammatory cytokine whose expression level increases after ischaemic stroke [55].

		IL1A	Interleukin 1 alpha	- Encodes a member of the interleukin 1 cytokine family and is involved in various immune response and inflammatory processes. IL1 is induced rapidly in response to cerebral ischaemia and leads to neuronal injury [58].
		IL6	Interleukin 6	- Encodes a cytokine that functions in inflammation. After ischaemic stroke, inflammatory cells can secret cytokines such as IL6. IL6 is considered as a deteriorator of stroke outcome [59].
		TNFRSF14	TNF receptor superfamily member 14	- Encodes a member of the TNF (tumor necrosis factor) receptor superfamily that functions in signal transduction pathways which activate inflammatory and inhibitory T-cell immune response. Activation of TNFRSF14 acts as a T-cell stimulatory signal that results in induction of pro-inflammatory genes [60].
		TNFRSF10D	TNF receptor superfamily member 10D	- Encodes a member of the TNF receptor superfamily. This receptor has been shown to play an inhibitory role in TRAIL-induced cell apoptosis [61].
		TNF	Tumor necrosis factor	- Encodes a multifunctional proinflammatory cytokine that belongs to the tumor necrosis factor (TNF) superfamily. It is mainly secreted by macrophages. TNF production is increased in response to brain injury by ischaemia [62].
		TNFRSF12A	TNF receptor superfamily member 12A	- Encodes a member of the TNF receptor superfamily. Its expression is induced by brain ischaemia/reperfusion injury [63].
Integrin		ITGB5	Integrin subunit beta 5	- Encodes a beta subunit of integrin. Integrins are integral cell-surface receptors that participate in cell adhesion as well as cell-surface mediated signaling. - Ischaemic stroke causes active angiogenesis[64]. Activation of endothelia cells is an early stage of angiogenesis and is characterized by expression of new cell surface proteins (e.g., integrins) [65].
		ITGAX	Integrin subunit alpha X	- Encodes the integrin alpha X chain protein. - Ischaemic stroke increased the expression of ITGAX [66].
		CD47	CD47 molecule	- Encodes a membrane protein, which is involved in the increase in intracellular calcium concentration that occurs upon cell adhesion to extracellular matrix. - Ischaemia does not upregulate total brain levels of CD47 in mice [67].
		ITGAM	Integrin subunit alpha M	- Encodes the integrin alpha M chain. ITGAM is important in adherence of neutrophils and monocytes to stimulated endothelium in ischaemic brain injury [68]. - ITGAM expression is up-regulated in response to ischaemia [69].
ECM proteins		COL6A1	Collagen type VI alpha 1 chain	- Collagens are a superfamily of proteins that play a role in maintaining the integrity of various tissues. - Ischaemic stroke degrades extracellular matrix such as collagen and breaks down blood-brain-barrier [70] .

		FN1	Fibronectin 1	- This gene encodes fibronectin, a glycoprotein present in plasma, at the cell surface, and in extracellular matrix. It promotes cell-cell and cell-matrix interactions [71]. - Cerebral ischaemia results in the continuous disappearance of basal membrane components [72].
		LAMA4	Laminin subunit alpha 4	- Laminins, a family of extracellular matrix glycoproteins, are the major noncollagenous constituent of basement membranes. - Focal cerebral ischaemia induces active proteases that degrade microvascular matrix proteins including laminin [73].
		LAMA2	Laminin subunit alpha 2	- Laminins, a family of extracellular matrix glycoproteins, are the major noncollagenous constituent of basement membranes. - Focal cerebral ischaemia induces active proteases that degrade microvascular matrix proteins including laminin [73].
		COL4A1	Collagen type IV alpha 1 chain	- Encodes a type IV collagen alpha protein which is a major component of the vascular basement membrane (BM) in the brain [74]. - Mutations in COL4A1 causes cerebrovascular diseases including intracerebral hemorrhages [75]. - Ischaemic stroke degrades extracellular matrix such as collagen and breaks down blood-brain-barrier [70] .
MMP		MMP12	Matrix metallopeptidase 12	- Encodes a member of the peptidase M10 family of matrix metalloproteinases (MMPs). MMPs are markers for the pathological ischaemic stroke processes. MMPs attack the extracellular matrix (ECM) around the blood vessels as well as the matrix around neurons, facilitating neural cell death. It disrupts the blood-brain barrier [76]. - MMP12 level is upregulated at 24 and 72 hours after stroke [77].
		MMP2	Matrix metallopeptidase 2	- Encodes a member of the peptidase M10 family of matrix metalloproteinases (MMPs). - Focal ischaemia increases MMP2 activities in human brain [78].
		TIMP1	TIMP metallopeptidase inhibitor 1	- Encoded a protein that is a natural inhibitor of the matrix metalloproteinases (MMPs), a group of peptidases involved in degradation of the extracellular matrix. - TIMP1 expression is similar in both control and ischaemia brain tissue at both 1 and 5 days after ischaemia stroke in rat brain [79].
Cell adhesion		SPARC	Secreted protein acidic and cysteine rich	- Encodes a cysteine-rich acidic matrix-associated protein that regulates growth factors and the assembly of the extracellular matrix. - Under homeostatic conditions, mature microglia express SPARC. In a ischaemic stroke model, microglia downregulate SPARC expression after injury [77].
		ANXA2	Annexin A2	- Encodes a member of the annexin family that is a cell-surface receptor for both plasminogen (the inactive precursor of plasmin), and its activator, tPA. The tPA-annexin A2-plasminogen triple complex enables lower concentrations of tPA to convert plasminogen to plasmin very efficiently with a maxim of 60-fold increase in catalytic efficiency compared with the same amount of tPA alone [80].

		AKAP12	A-kinase anchoring protein 12	- Encodes a member of the A-kinase anchor proteins (AKAP) family. AKAP12 regulates cell motility and invasion. - During the CNS repair process, it attracts candidate molecule that integrates scar r formation as a result of complex events such as the immune response, migration of various cells, and tissue remodeling [81].
		EGFR	Epidermal growth factor receptor	- Encodes a protein that is a receptor for members of the epidermal growth factor family. - Activation of EGFR has been shown to trigger quiescent astrocytes into reactive astrocytes [82] and mediates the EGF-induced chemotactic and chemokinetic migration of microglia [83] in response to several neural injuries including ischaemic stroke.
		TNC	Tenascin C	- Encodes an extracellular matrix protein with a spatially and temporally restricted tissue distribution. - TNC exerts diverse functions through direct binding to cell surface receptors, other matrix proteins, and soluble extracellular factors [84].
		CTGF (CCN2)	Cellular communication network factor 2	- Encoded a protein that plays a role in cell adhesion in many cell types and is related to platelet-derived growth factor. It strongly stimulates expression the extracellular matrix proteins collagen type I and fibronectin as well as of integrin α5 by fibroblasts. - In the brain, CTGF expression is induced by brain injury, accompanied by an increased production of fibronectin. It plays a role in postlesional restructuring of the hippocampus, where it possibly participates in glial scar formation [85].
Neurite		NES	Nestin	- Encodes a member of the intermediate filament protein family expressed in neurons and glial cells [86]. - The expression of nestin in glial, neuronal and ependymal cells increases throughout the microvasculature in the ischaemic rat model [87].
		NFLA	neurofilament, light polypeptide	- Encodes a light chain neurofilament protein that maintains neuronal caliber. Mutations in this gene cause Charcot-Marie-Tooth disease, disorders of the peripheral nervous system [88]. - Ischaemic stroke patients show higher expression level of this protein when compared to those of the healthy control group [89].
		GPRIN1	G protein regulated inducer of neurite outgrowth 1 (GRIN1)	- Encodes a protein that are enriched in the growth cones of neurites and involved in neurite extensions [90].
		RTN4	Reticulon 4 (Nogo)	- Encodes a family of reticulon that inhibits neurite outgrowth [91]. - RTN4 expression is upregulated in response to ischaemia [92].
Synaptogenesis		GAP43	Growth associated protein 43	- Encodes a protein that is highly expressed in axon growth cone and presynaptic terminal [93]. It is a synaptogenesis indicator [94]. - GAP43 expression is upregulated shortly after ischaemia in the brain [95].
		SIRPA	Signal regulatory protein alpha	- Encodes a transmembrane protein that is predominantly expressed in neurons, dendritic cells, and macrophages. It drives presynaptic maturation in an activity-dependent fashion [96]. - This protein protects neurons from oxidative stress after brain ischaemia [97].

		PANX1	Pannexin 1	- Encodes a protein of the innexin family members that comprise the structural components of gap junctions [98]. It also regulates synaptic plasticity [99]. - The expression of panx1 is activated by ischaemia [100].
		CDH2	Cadherin 2 (neuronal cadherin)	- Encodes a member of the cadherin superfamily that is involved in calcium-dependent cell adhesion molecule and glycoprotein [101]. It is involved in early brain morphogenesis, long-term potentiation, synaptic plasticity and synaptogenesis [102]. - CDH2 expression is significantly upregulated 6 hour after ischaemia [103].
		THBS1	Thrombospondin 1	- Encodes an adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions, which can bind to extracellular matrix proteins. This gene family is known as key regulators of synaptogenesis in the central nervous system [104]. - THBS1 expression increases after focal ischaemia. It is necessary for synaptogenesis after stroke [105].
		SYN1	Synapsin I	- Encodes a neuronal phosphoprotein associate with the cytoplasmic surface of synaptic vesicles. Expression of this gene is related to synaptogenesis and neurotransmitter release [106]. - The level of syn1is highly related to dentate neurogenesis and synaptogenesis after hippocampal injury caused by global ischaemia [107].
Synaptic plasticity		DLG4 (PSD95)	Discs large MAGUK scaffold protein 4	- Encodes a member of the membrane-associated guanylate kinase family and is recruited into N-methyl-D-aspartate (NMDA) receptor, a typical excitatory amino-acid neurotransmitter.[108] -Disrupting the interaction of NMDA receptors with DLG4 can suppress excitotoxicity and ischaemia brain damage [109].
		NLGN3	Neuroligin 3	- Encodes a member of a family of neuronal cell surface proteins. It is a synaptic cell-adhesion molecule that is required for synapse function. It affects the trans-synaptic activation of synaptic transmission. Dysfunction of neuroligin impairs the properties of synapses and disrupts neural networks without completely abolishing synaptic transmission [110].
		LIF	LIF interleukin 6 family cytokine	- Encodes a protein that is a pleiotropic cytokine with roles in several different systems. It has profound effects on the survival and maintenance of motor neurons [111] -It activates Notch pathway after ischaemia which substantially increases neural progenitor cell proliferation [112].
		VGF	VGF nerve growth factor inducible	- This gene is specifically expressed in a subpopulation of neuroendocrine cells. Brain-derived neurotrophic factor (BDNF)-induced synaptic strengthening in cultured hippocampal neurons revealed increased expression of VGF, suggesting VGF neuropeptides may regulate synaptic function. C-terminal VGF peptides acutely increased synaptic charge in a dose-dependent manner [113].

		CAMK2A	Calcium/calmodulin dependent protein kinase II alpha	- Belongs to the serine/threonine protein kinases family, and to the Ca(2+)/calmodulin-dependent protein kinases subfamily. Calcium signaling is crucial for several aspects of plasticity at glutamatergic synapses. -N-methyl-D-aspartate (NMDA) receptors that bind to CAMKII dramatically reduces long-term potentiation (LTP, a form of synaptic plasticity) [114].
Neurotransmitters		SLC1A2 (GLT1)	Solute carrier family 1 (glial high affinity glutamate transporter), member 2	- Encodes a membrane-bound transporter protein that clears excessive glutamate in the brain, which protects neurons from excitotoxicity [115]. - GLT1 expression is upregulated in the ischaemic brain [116,117].
	Glutamate	GRM1 (mGluR1)	Glutamate metabotropic receptor 1	- Encodes a G-protein coupled receptor for glutamate [118]. - Related to both neuroprotective and neurotoxic during ischaemic damage in the brain [119]. - GRM1 Can serve as an indicator of brain pathology due to its dynamic changes during brain activity [120].
		GLUL	Glutamate-ammonia ligase (glutamine synthase)	- Encodes a protein that catalyzes the synthesis of glutamine from glutamate and ammonia, which controls excitotoxicity by uptake of excessive glutamate during brain injury [121,122].
		VAMP2	Vesicle associated membrane protein 2 (synaptobrevin 2)	- Encodes a presynaptic protein that regulates docking and/or fusion of synaptic vesicles, which is related to synaptic transmission [123]. - The formation of presynaptic protein complex is mediated by blockade of glutamate receptors [124].
		CACNG5	Calcium voltage-gated channel auxiliary subunit gamma 5	- Encodes a type II transmembrane AMPA receptor regulatory protein (TARP) that regulates trafficking and channel gating of the glutamate receptors, specifically AMPA [125].
	GABA	ABAT	4-aminobutyrate aminotransferase	- Encodes an enzyme that catalyzes the conversion/breakdown of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter [126].
		GABRB1	Gamma-aminobutyric acid type A receptor beta 1 subunit (GABA (A) receptor, beta 1)	- Encodes a multisubunit chloride channel that mediates the rapid inhibitory synaptic transmission in the brain [127]. - GABA acts postsynaptically through GABA A receptors and the gating of Cl channels to counter membrane depolarization and to limit calcium entry during ischaemia in the brain [128].
EC-EC junctions		CDH2	Cadherin 2	- Encodes a classical cadherin and member of the cadherin superfamily. - Adherens junctions (AJs) consist of cadherin proteins and hold the cells together giving the tissue structural support. Disruption of AJs leads to blood-brain-barrier (BBB) disruption [129]. - Ischaemic stroke disrupts BBB integrity [130].
		CLDN3	Claudin 3	- Claudin proteins contributes to the physiological “seal” of the tight junction. Claudin-3 influences barrier function. - Ischaemic stroke disrupts BBB integrity and disruption of tight junction protein complexes is a hallmark of BBB disruption [130].

		GJA1 (CX43)	Gap junction protein alpha 1	- Encoded a protein that is a component of gap junctions. Gap junctions are essential for BBB integrity. They regulate the paracellular permeability of BBB [131]. - Ischaemic stroke disrupts BBB integrity [130]. Targeted gene knockout of GJA1 results in impaired gap junctional coupling and attenuation of intercellular calcium signaling [132].
		OCLN	Occludin	- Encodes an integral membrane protein that is required for regulation of the tight junction paracellular permeability barrier. Occludin is a critical transmembrane regulator of BBB functional integrity in vivo [130]. - In a focal cerebral ischaemia model by transient middle cerebral artery occlusion in male rats, the expression of occludin is significantly down-regulated [54].
		ZO-1 (TJP1)	Tight junction protein 1.	- Encodes a member of the membrane-associated guanylate kinase (MAGUK) family of proteins, and acts as a tight junction adaptor protein t. ZO-1-transmembrane protein interaction is critical to tight junction stability and function. - In a focal cerebral ischaemia model by transient middle cerebral artery occlusion in male rats, the expression of ZO-1 is significantly down-regulated [133].
		CLDN5	Claudin 5	- Claudin proteins contributes to the physiological “seal” of the tight junction. Claudin-5 is the predominant claudin isoform that limits paracellular diffusion of small molecules. -Ischaemic stroke disrupts BBB integrity and disruption of tight junction protein complexes is a hallmark of BBB disruption [130]. - In a focal cerebral ischaemia model by transient middle cerebral artery occlusion in male rats, the expression of claudin-5 is significantly down-regulated [133].
Vasoconstriction		AGTR1	Angiotensin II receptor type 1	- It is an important effector controlling blood pressure and volume in the cardiovascular system. AGTR1 expression increases immediately after ischaemia-reperfusion [134].
		EDNRB	Endothelin receptor type B	- Encoded a G protein-coupled receptor which activates a phosphatidylinositol-calcium second messenger system. EndrB is capable of inducing vasoconstriction in mammals [135]. - The expression of EndrB is significantly upregulated cerebral ischaemia induced by right middle cerebral artery occlusion in rat [136].
		TPM1	Tropomyosin 1	- This gene is a member of the tropomyosin family of highly conserved, widely distributed actin-binding proteins involved in the contractile system. - Tropomyosin expression increases after rat traumatic brain injury [137].
		MYLK (MLCK)	Myosin light chain kinase	- Encodes myosin light chain kinase which phosphorylates myosin regulatory light chains to facilitate myosin interaction with actin filaments to produce contractile activity. -MYLK expression is elevated after cerebral ischaemia/reperfusion injury [138].

Adhesion mol. for recruiting immune cells		PECAM1	platelet and endothelial cell adhesion molecule 1	- Encodes a member of the immunoglobulin superfamily and is expressed on the surface of vascular endothelial cells. PECAM-1 is an endothelial cell-cell adhesion molecule that is involved in angiogenesis [139]. - PECAM-1 is a key participant in the adhesion cascade leading to extravasation of leukocytes during the inflammatory process like ischaemic stroke [140,141].
		CXCR3	C-X-C motif chemokine receptor 3	- Encodes a G protein-coupled cell surface receptor with selectivity for three chemokines: CXCL9, CXCL10, and CXCL11. Its major function is to selectively recruit immune cells at inflammation sites [142]. - Interactions of CXCR3-binding chemokines with CXCR3 receptor, which has been detected on human microvascular endothelial cells only when they are in a proliferative stage, inhibits angiogenesis [142].
		ICAM1	Intercellular adhesion molecule 1	- Encodes a cell surface glycoprotein which is typically expressed on endothelial cells and cells of the immune system. Expression of ICAM1 contributes to immune cells adhesion to endothelial and other cells. Increased expression of ICAM1 is found in immune reactions [143]. - Ischaemic stroke induces upregulation of ICAM-1. After focal brain ischaemia, leukocytes adhere to the perturbed endothelium and are believed to aggravate reperfusion injury [144].
		CD44	CD44 molecule	- Encodes a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion and migration. It plays an important role in lymphocyte adhesion to inflamed endothelium [145]. - Cerebral ischaemia induces CD44 expression [146].
Pericyte markers	Reactive	CSPG4	Chondroitin sulfate proteoglycan 4 (NG2)	- Known as a conventional pericyte marker [147,148]. - CSPG4 is upregulated in pericytes following chronic hypoxia [149].
		PDGFRB	Platelet derived growth factor receptor beta	- Known as a conventional pericyte marker [147,148]. - Expression level of this gene in brain pericytes is gradually increased in the ischaemic stroke model [150].
		ITGA5	Integrin subunit alpha 5 (CD49e)	- Encodes a protein of integrin alpha chain family that associates with the beta 1 subunit to form a fibronectin receptor [151]. - ITGA5 is identified as a gene of mouse kidney pericytes that mediates vascular permeability [152].
		DES	Desmin	- Encodes a protein that maintains the structure of sarcomeres, which are necessary for muscles to contract [153]. - DES is expressed both in pericytes and vascular smooth muscle cells [154].
		RGS5	Regulator of G protein signaling 5	- Encodes a GTPase activating protein involved in recruitment of pericytes during angiogenesis [155]. - Upregulated in pericytes in response to ischaemic injury [156]. - Loss of this gene is related to neural protection during stroke [157].

		EPHA2	EPH receptor A2	- Encodes an ephrin receptor subfamily of the protein-tyrosine kinase family involved in tubular network formation [158]. - EPHA2 is involved in BBB damage and neuronal death after ischaemic stroke [159].
		ACTA2	Actin alpha 2, smooth muscle (α-SMA)	- Encodes a contractile and cytoskeletal protein that is expressed both in pericytes and vascular smooth muscle cells [160]. - Upregulated in ischaemic retina [161].
	Pan	CD248	CD248 (endosialin)	- Encodes a protein family of C-type lectin transmembrane receptors involved in cell–cell adhesion and host defense [162]. - The expression of this transmembrane glycoprotein is restricted to pericytes in the vasculature [163].
		ANPEP	Alanyl aminopeptidase, membrane	- Encodes a cell-membrane metalloprotease involved in metabolism of regulatory peptides and regulation of angiogenesis [164]. - ANPEP is expressed in pericytes, epithelial cells, macrophages, granulocytes, and synaptic membranes of neural stem cells [165].
PC-EC interaction		MCAM (CD146)	Melanoma cell adhesion molecule	- CD146 is constitutively expressed in the pericytes of several organs and functions as a component of endothelial junctions to reduce the paracellular permeability of peripheral ECs. It is required for BBB development by dynamically coordinating pericyte-EC communication during embryogenesis [166]. - Loss of CD146 results in BBB breakdown [166].
		ERBB2	Erb-b2 receptor tyrosine kinase 2	-Encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. - Activation of epidermal growth factor receptors (EGFRs) erbB1 and erB2 is involved in maintaining and stabilizing mature vessels by promoting interactions between ECs and pericytes [167] .
		EFNB2	Ephrin B2	- Encodes a member of the ephrin (EPH) family. Ephrin B receptors (EphB) and ephrin B ligands play a critical role in the regulation of developmental angiogenesis and pericyte-endothelial interactions during vascular assembly. Ephrin-B2/EphB4 signaling controls pericyte directional migration and adhesion to maturing vessels [168]. - Focal cerebral ischaemia downregulates the expression of Ephrin B2 [169].
Astrocyte reactive markers	Pan	CXCL10	C-X-C (Cys-X-Cys) motif chemokine ligand 10 (Interferon gamma-induced protein 10 (IP-10))	- Encodes a chemokine of the CXC subfamily and ligand for the receptor CXCR3 [170]. - Expression level of CXCL10 is higher in ischaemic stroke patients than in healthy controls [171].
		VIM	vimentin	- Encodes a type III intermediate filament protein, which is highly expressed in response to the injury in the brain [172].
		LCN2	lipocalin 2 (oncogene 24p3)	- Encodes a protein of the lipocalin family that transports lipids or steroid hormones and mediates innate immunity by controlling bacterial growth [173]. - Rapidly upregulated and quickly attenuated during inflammation or ischaemia in the brain [174].
	A1	C3	complement C3	- Encodes an immune regulator of the complement pathway that mediates host defense to infection and tissue homeostasis [175].

				- Specifically upregulated in A1 (inflammation), not in A2 (ischaemia) reactive astrocytes [176].
		C1R	complement C1r	- Encodes a member of the peptidase S1 protein family and a proteolytic subunit in the complement system C1 complex, which is highly upregulated in A1 reactive astrocytes [174].
	A2	CD109	CD109	- Encodes a glycosyl phosphatidylinositol (GPI)-linked glycoprotein that localizes to the surface of platelets, activated T-cells, and endothelial cells [177,178]. - Markers of A2 reactive astrocytes [174,176].
		EMP1	epithelial membrane protein 1	- Encodes a member of membrane glycoprotein family involved in cell-cell interactions and the control of cell proliferation [179]. - Markers of A2 reactive astrocytes [174].
		TGM1	transglutaminase 1	- Encodes a membrane protein that induces crosslinking of proteins by forming an alkylglutamine in the protein [180]. - Markers of A2 reactive astrocytes [174].
		TM4SF1	transmembrane 4 L six family member 1	- Encodes a transmembrane 4 superfamily with four hydrophobic domains [181]. - Markers of A2 reactive astrocytes [182].
AC-neuron interaction		NLGN3	Neuroligin 3	- Encodes a member of neuronal cell surface proteins family. Neuroligin proteins expressed by cortical astrocytes, control astrocyte morphogenesis through interactions with neuronal neurexins [183].
		FABP7	Fatty acid binding protein 7	- Encodes a small, highly conserved cytoplasmic protein that bind long-chain fatty acids and other hydrophobic ligands. Astrocyte-expressed FABP7 regulates dendritic morphology and excitatory synaptic function of cortical neurons [184]. - FABP7 expression is increased within different hippocampal sub-regions in response to cerebral ischaemia in young adult monkeys [185].
		S100A6	S100 calcium binding protein A6	- Encoded a member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs. S100A6 is more selectively expressed in astrocytes closely linked to damaged axons of motoneurons [186].
		S100B	S100 calcium binding protein B	- S100B, synthesized in considerable amounts in astrocytes, modulates long-term synaptic plasticity [187]. - Ischaemic and hemorrhagic strokes lead to release of protein S100B into the blood. It is the marker of brain damage during stroke [188].
		IFITM3	Interferon induced transmembrane protein 3	- Lipopolysaccharide (LPS) treatment can induce IFITM3 expression in astrocyte [189]. - Astrocyte expressing IFITM3 mediates long-lasting neuronal impairments [190].
Microglia reactive markers	Pan	CD68	CD68 molecule	- CD68 is a lysosomal membrane marker and stains microglia in a highly active, phagocytizing state [191]. - Stroke is a powerful stimulus that triggers microglia activation [192].

		IBA-1	(Allograft inflammatory factor 1) Ionized calcium-binding adapter molecule 1	- IBA-1 is a novel calcium-binding protein and is specifically expressed in microglia in the brain. - Expression of IBA-1 is upregulated during cerebral ischaemia [193].
	M1	CD86	CD86 molecule	- Microglia activated by ischaemic stroke exhibit a spectrum of phenotypes, release both pro- (M1 microglia) and anti-inflammatory (M2 microglia) mediators, and function to either exacerbate ischaemic injury or help repair depending on different molecular signals the microglial receptors receive [192]. - Encodes a type I membrane protein that is a member of the immunoglobulin superfamily. CD86 is a marker for M1 microglia (proinflammatory cellular state) [193]. - Ischaemic stroke increased the expression of CD86 [194].
		BIRC3	Baculoviral IAP repeat containing 3	- Encodes a member of the IAP family of proteins that inhibit apoptosis by binding to tumor necrosis factor receptor-associated factors TRAF1 and TRAF2. BIRC3, a marker for M1 microglia [195], is induced by ischaemic stroke [196].
		CD40	CD40 molecule	- Encoded a protein that is a receptor on antigen-presenting cells of the immune system and is essential for mediating a broad variety of immune and inflammatory responses. CD40 is a marker for M1 microglia [193] and its expression is upregulated in acute cerebral ischaemia [197].
	M2a	CD206 (MRC1)	mannose receptor C-type 1	- Encoded a type I membrane receptor that mediates the endocytosis of glycoproteins by macrophages - M2 microglia are further characterized into sub-classification, M2a, M2b, and M2c [198]. CD206 is a marker for M2a microglia (inflammation resolution and phagocytosis state) [199]. It is exclusively found in the ischaemic core to promote tissue repair [200].
		CD200R1	CD200 receptor 1	- Encodes a receptor for the OX-2 membrane glycoprotein. CD200R expression is modulated by IL-4 [201], which is a particularly important cytokine for M2a skewing of microglia [198].
		CD33	CD33 molecule	- CD33 is a member of the sialic acid-binding immunoglobulin-like lectin (SIGLEC) family of receptors and expressed largely in microglia [202]. - It functions to limit immune activation and phagocytosis [203].
	M2b	CD64a (CD64/ FCGR1A)	Fc fragment of IgG receptor Ia	- Encodes a protein that is a high-affinity Fc-gamma receptor and plays an important role in the immune response. - M2b microglia (clearance of reactive oxygen and nitrogen species released during M1 activation) are induced by ligation of immunoglobulin Fc gamma receptors including CD64 and CD32 [204].
		CD32a (CD32/ FCGR2A)	Fc fragment of IgG receptor IIa	- Encodes one member of a family of immunoglobulin Fc receptor genes found on the surface of many immune response cells. - M2b microglia are induced by ligation of immunoglobulin Fc gamma receptors including CD64 and CD32 [204].

	M2c	CD163	CD163 molecule	- Encodes a member of the scavenger receptor cysteine-rich (SRCR) superfamily. CD163 is considered as a marker for both M2a and M2c microglia (wound healing) [205].
Immune receptors		SLAMF9	SLAM family member 9	- Encodes a cell surface molecule that is a member of the signaling lymphocytic activation molecule family. - SLAMF9 expression is upregulated in intracerebral hemorrhage stroke [206].
		CD36	CD36 molecule	- CD36 is a class B scavenger receptor and is a surface glycoprotein. It is involved in the cytotoxicity associated with inflammation. - CD36 expression was increased in the ischaemic brain. It contributes to increase in reactive oxygen species and tissue injury [207].
		PILRA	Paired immunoglobulin like type 2 receptor alpha	- Encodes a cell surface inhibitory receptor that recognizes specific O-glycosylated proteins and is expressed on various innate immune cell types including microglia. - PILRA is a negative regulator of inflammation, with knockout macrophages showing increased production of cytokines (IL6, IL-1b, KC, MCP-1) and increased infiltration of monocytes and neutrophil [208].
		CD85c (LILRB5)	Leukocyte immunoglobulin like receptor B5	- Encodes a member of the leukocyte immunoglobulin-like receptor (LIR) family that belongs to the subfamily B class of LIR receptors. - CD85c modulates immune cell activity [209].
		HAVCR2 (TIM3)	Hepatitis A virus cellular receptor 2	- Encoded a protein that belongs to the immunoglobulin superfamily and TIM family of proteins. This protein is a Th1-specific cell surface protein that regulates macrophage activation. - TIM3 expression is involved in inflammation and is induced by ischaemic stroke [210].
		GPR84	G protein-coupled receptor 84	- GPR84 mediates the involvement of medium-chain free fatty acids in the inflammatory processes provoked by the immune system [211]. - GPR84 expression was upregulated in stroke patients [212].
		MSR1	Macrophage scavenger receptor 1	- Encodes the class A macrophage scavenger receptors. It mediates the internalization of damage-associated molecular patterns and reduces inflammation. - MSR1 expression was found to be elevated 3 and 6 days after ischaemic stroke in mice [213].
		MARCO (SR-A6)	Macrophage receptor with collagenous structure	- Encodes a member of the class A scavenger receptor family and is part of the innate antimicrobial immune system. - Bacteria or bacterial lipopolysaccharide (LPS) can stimulate SR-A6 expression [214].
		CD155 (PVR)	PVR cell adhesion molecule	- Encodes a transmembrane glycoprotein belonging to the immunoglobulin superfamily. - CD155 is a broadly expressed receptor that exerts immune regulator functions. It is induced in T cells upon their activation [215].
		CD14	CD14 molecule	- Encodes a surface antigen that is preferentially expressed on monocytes/macrophages. - The expression of CD14 is induced by ischaemic stroke in mice [216].

Chemoattractant		CXCL9	C-X-C motif chemokine ligand 9	- Encodes a protein that binds to C-X-C motif chemokine 3 (CXC3) and is a chemoattractant for lymphocytes. Chemokines are a family of small proteins that play an important role in pro-inflammatory signals and the recruitment and activation of leukocytes [197]. - M1 microglia express CXCL9 and promote immune response during ischaemic stroke [198]. The expression of CXCL9 is elevated 24 h after ischaemia-reperfusion injury [81].
		CCL8	C-C motif chemokine ligand 8	- This chemokine is a member of the CC subfamily. - In cerebral tissue of multiple sclerosis patients, high expression of chemokines such as CCL8 and CXCL1 has been shown [197].
		CXCL2	C-X-C motif chemokine ligand 2	- This chemokine is part of a chemokine superfamily that encodes secreted proteins involved in immune regulatory and inflammatory processes. - CXCL2 expression is induced in ischaemic brain for the recruitment of neutrophil [199].
		IL8	C-X-C motif chemokine ligand 8	- Encodes a member of the CXC chemokine family and is a major mediator of the inflammatory response. -CXCL8 level is upregulated for ischaemic stroke [200].
		CXCL1	C-X-C motif chemokine ligand 1	- Encodes a member of the CXC subfamily of chemokines that plays a role in inflammation and as a chemoattractant for neutrophils. - CXCL1 expression is upregulated in ischaemic brain [201].
TLR		TLR2	Toll like receptor 2	- Toll-like receptors (TLRs) are the key components of the innate immune system and they are involved in the recognition of different ligands generated by brain ischaemia [202]. - TLR2 is upregulated after focal cerebral ischaemia and triggers downstream signaling cascade and proinflammatory gene transcription [203]
		TLR5	Toll like receptor 5	- Participates in the inflammatory reaction. Its expression increases after focal ischaemia [204].
		TLR3	Toll like receptor 3	-TLR3 is not found to have association with outcome or infarct volumes in ischaemic stroke patients [205].
		TLR4	Toll like receptor 4	- Participates in the inflammatory reaction. Its expression increases after focal ischaemia [204].
		MYD88	MYD88 innate immune signal transduction adaptor	- Encodes a cytosolic adapter protein that plays a central role in the innate and adaptive immune response. It acts as an adaptor protein in the signaling of the Toll-Like receptors (TLRs) and the interleukin-1 (IL-1) receptor. MYD33 encodes the adaptor necessary for the initiation of TLR2 signaling [206]. - MYD88 expression increases after ischaemic stroke [207].
NF-κB signal		NFKB1	Nuclear factor kappa B subunit 1	-NFKB factors act as regulators of growth, differentiation and adaptive responses to extracellular signals in the central nervous system. - After an ischaemic insult to the brain, NFKB is rapidly activated in neurons and glial cells and acts as a regulator of inflammation and apoptosis [208].
		IRF1	Interferon regulatory factor 1	- Encoded a transcriptional regulator and tumor suppressor, serving as an activator of genes involved in both innate and acquired immune

				responses. IRF1 promoter contains one NF-κB site [209]. - Ischaemic stroke induces IRF-1 expression [210].
		BCL3	Baculoviral IAP repeat containing 3	- Encodes a member of the IAP family of proteins that inhibit apoptosis by binding to tumor necrosis factor receptor-associated factors TRAF1 and TRAF2. BCL3 is a member of the IκB family what carries multiply domains necessary for the interaction with the NF-κB family members [211]. - Expression of BCL3 is increased in hypoxia which accelerates vascular repair of endothelial colony-forming cells on ischaemic injury [212].
		RUNX1	Runt related transcription factor 1	- RUNX1 expression is induced after brain injury. It is expressed in proliferative and activated microglia [213]. - RUNX1 is a cytoplasmic attenuator of NF-κB signaling pathway [214] .
NLR signal		NLRP3	NLR family pyrin domain containing 3	- Encodes a protein that interacts with the apoptosis-associated speck-like protein PYCARD/ASC. NLRP3, PYCARD, and caspase-1 together form NLRP3 inflammasome which promotes inflammation, the immune response, and apoptosis once activated [215]. -NLRP3 expression is significantly increased after cerebra ischaemia. It contributes to microglia activation and brain microvessel endothelial cell dysfunction [216].
		PYCARD (ASC)	PYD and CARD domain containing	- Encodes an adaptor protein that is composed of two protein-protein interaction domains: PYC and CARD. PYCARD serves as the adaptor for NLRP3 inflammasome. - Ischaemic stroke activates NLRP3 inflammasome with the upregulation of PYCARD [215].
MHC class II mol.		HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	- Belongs to the HLA class II beta chain paralogs. The class II molecule is a heterodimer consisting of an alpha (DRA) and a beta chain (DRB), both anchored in the membrane. It plays a central role in the immune system by presenting peptides derived from extracellular proteins to immune cells. - MHC class II molecules are induced by ischaemic stroke [217].
		HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	- Belongs to the HLA class II beta chain paralogs. The class II molecule is a heterodimer consisting of an alpha (DRA) and a beta chain (DRB), both anchored in the membrane. It plays a central role in the immune system by presenting peptides derived from extracellular proteins to immune cells. - MHC class II molecules are induced by ischaemic stroke [218].
		HLA-DRA	Major histocompatibility complex, class II, DR alpha	- Belongs to the HLA class II alpha chain paralogues. - MHC class II molecules are induced by ischaemic stroke [217].
		HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	- Belongs to the HLA class II beta chain paralogs. - MHC class II molecules are induced by ischaemic stroke [217].

Purinergic receptors		P2RX4	Purinergic receptor P2X4	- Encodes a protein family of purinoceptors for ATP. This is a ligand-gated ion channel with a function of high calcium permeability [218,219]. - P2RX4 is highly upregulated in the ischaemic brain [220].
		P2RY2	Purinergic receptor P2Y2	- Encodes a protein family of P2 receptors, which is activated by extracellular nucleotides and subdivided into P2X ligand-gated ion channels and P2Y G-protein coupled receptors [219,221]. - This gene could be related to the risk of ischaemic stroke in the Han Chinese population [222].
		P2RX7	Purinergic receptor P2X7	- Encodes a protein family of purinoceptors for ATP. This is a ligand-gated ion channel with a function of ATP-dependent lysis of macrophages through the formation of membrane pores permeable to large molecules [219,223]. - Suppression of this gene can prevent ischaemic damage in the brain [224].
		P2RY12	Purinergic receptor P2Y12	- Encodes a protein family of G-protein coupled receptors. This gene is involved in platelet aggregation [219,225]. - P2RY12 is involved in microglial activation during ischaemia [226].
		P2RY1	Purinergic receptor P2Y1	- Encodes a protein family of G-protein coupled receptors. This gene functions as a receptor for extracellular ATP and ADP. In platelets binding to ADP leads to mobilization of intracellular calcium ions via activation of phospholipase C, a change in platelet shape [219,227]. - This receptor expressed in astrocytes may regulate the cytokine/chemokine response after ischaemia [228].
Immune Regulation		FOSL1	FOS like 1, AP-1 transcription factor subunit	- Amplifies immune response and stimulates the expression of inflammatory genes [229]. - FOSL1 expression is not affected by ischaemia [230].
		AHR	Aryl hydrocarbon receptor	- Encodes a transcriptional regulator involved in adaptive xenobiotic response and immune response [231]. - AHR expression is increased in ischaemic stroke [232].
		KLF5	Kruppel like factor 5	- Encodes a member of the Kruppel-like factor subfamily of zinc finger proteins. It is a transcriptional activator that binds directly to a specific recognition motif in the promoters of target genes. - KLF5 can activate T cell [233]. KLF5 is induced in reactive astrocytes from mouse brains following ischaemic stroke [234].
		IRF8	Interferon regulatory factor 8	- Encodes a transcription factor of the interferon regulatory factor (IRF) family. It is an immune cell-specific IRF family member. Irf8 $^{-/-}$ dendritic cells fail to produce proinflammatory cytokines [235]. - IRF8 expression is suppressed at the onset of stroke and is further decreased to 26% of the baseline at 72 h of ischaemia [236].
		IL10	Interleukin 10	- IL10 is a key immune regulator and acts as an anti-inflammatory cytokine. - Patients have significantly lowered IL-10 serum levels soon after the acute event, with a slight increase at the seventh day [237].

Supplementary Table 3 | Functional characteristics and relevant references of the genes in **Figure 5**.

Gene name	Protein name	Characteristics
ABAT	4-aminobutyrate aminotransferase	- Encodes an enzyme that catalyzes the conversion/breakdown of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter [238].
ACHE	Acetylcholinesterase	- Hydrolyzes the neurotransmitter, acetylcholine at neuromuscular junctions and brain cholinergic synapses, and thus terminates signal transmission. - Shares a high sequence homology with neuroligins which critically participate in excitatory synaptic maturation and maintenance [239].
ADORA1	Adenosine A1 receptor	- ADORA1 activation causes a decrease in the rate of metabolism, allowing the cell to cope better with noxious stimuli [240]. - Controls synaptic plasticity [241]. - Inhibits inflammation, necrosis, and apoptosis after renal ischaemia-reperfusion injury in mice [242]. - ADORA1 negatively regulates adult neurogenesis while promoting astrogliogenesis [243]. - Belongs to the G-protein coupled receptor 1 family. A1-receptor activation inhibits many neurons postsynaptically by inducing or modulating ionic currents and presynaptically by reducing transmitter release [244].
ADORA2A	Adenosine A2a receptor	- Encodes a member of the G protein-coupled receptor superfamily. - Induces apoptosis [245]. - ADORA2A plays an important role in neurogenesis in hippocampus. It is highly expressed across the major adult neurogenesis-related regions of the brain [246]. - Has a non-redundant role in the attenuation of inflammation and tissue damage in vivo [247].
ALDH1A1	Aldehyde dehydrogenase 1 family member A1	- Encodes a protein that belongs to the aldehyde dehydrogenase family. It has been suggested as a marker for cancer stem cells [248].
ALK	ALK receptor tyrosine kinase	- Protects cells from apoptosis [249]. - Activated ALK triggers prolonged neurogenesis [250].
APBB1 (PE65)	Amyloid beta precursor protein binding family B member 1	- PE65 is a brain-enriched adaptor with several protein-binding domains. It recruits interactors to form functional complexes in different processes including promoting neurite outgrowth [251]. - Plays a role in regulation of transcription. Fe65 has been shown to modulate neurogenesis [252]. Overexpression of Fe65 prevents G1 to S cell cycle progression [253].
APOE	Apolipoprotein E	- Binds to lipoprotein receptor family which is involved in modulation of synaptic transmission [254]. - Promote synaptic plasticity. Apoe knockout mice shows impaired synaptic plasticity [255]. - Apoptosis induces APOE expression [256]. - Expressed in adult neural progenitor cells. In the APOE knockout mouse, neurogenesis was reduced while the number of neural progenitor cells acquiring a glial fate was increased [257].
APP	Amyloid beta precursor protein	- This gene encodes a cell surface receptor and transmembrane precursor protein. - Regulates neurite outgrowth. APP synthesis and axonal transport coincide with periods of axon elongation and synapse formation [258]. - APP has two separate domains: the soluble secreted APPs (sAPPα) and the PPP intracellular domain (AICD). sAPPα can protect neuron cells and promote neurogenesis. AICD can negatively modulate neurogenesis [259].

ARTN	Artemin	- Promotes the survival of neurons, the proliferation of sympathetic neuroblasts and increases the generation of new neurons in cultures [260].
ASCL1	Achaete-scute family bHLH transcription factor 1	- Encodes a member of the basic helix-loop-helix (BHLH) family of transcription factors that promotes neuronal migration in the cortex [261]. - Encodes a member of the basic helix-loop-helix (BHLH) family of transcription factors which is a master regulator of neurogenesis, activating a plethora of differentiation genes that coordinate neural commitment, subtype specification, and neuronal maturation [262].
BCL2	BCL2, apoptosis regulator	- Blocks programmed cell death and prevents apoptosis [263]. - BCL2 enhances neurogenesis and inhibits apoptosis of newborn neurons in adult rat brain following a transient middle cerebral artery occlusion [264].
BDNF	Brain derived neurotrophic factor	- Encodes a member of the nerve growth factor family of proteins. - Promotes neuronal differentiation and survival [265]. - Contributes to synaptic plasticity [266].
BMP2	Bone morphogenetic protein 2	- Encodes a secreted ligand of the TGF-beta superfamily of proteins that binds to TGF-beta receptors. - Potently inhibits neurogenesis both in vitro and in vivo and induces glia differentiation [267].
BMP4	Bone morphogenetic protein 4	- Encodes a secreted ligand of the TGF-beta superfamily of proteins that binds to TGF-beta receptors. - Potently inhibits neurogenesis both in vitro and in vivo and induces glia differentiation [267].
BMP8A	Bone morphogenetic protein 8A	- Encodes a secreted ligand of the TGF-beta superfamily of proteins that binds to TGF-beta receptors. - Middle cerebral artery occlusion dramatically induced BMP8A expression [268].
CDK5R1	Cyclin dependent kinase 5 regulatory subunit 1	- Encodes a neuron-specific activator of cyclin-dependent kinase 5 (CDK5) that is essential for radial migration and lamination of cortical neurons during the morphogenesis of the mammalian cerebral cortex [269].
CDK5RAP2	CDK5 regulatory subunit associated protein 2	- Encodes a regulator of CDK5 (cyclin-dependent kinase 5) activity. Cdk5rap2 is highly expressed in the neural progenitor pool and its loss results in a depletion of apical progenitors and increased cell-cycle exit leading to premature neuronal differentiation [270].
CHAT	Choline O-acetyltransferase	- Encodes an enzyme which catalyzes the biosynthesis of the neurotransmitter acetylcholine. - Expressed during neurogenesis [271].
CHRM2	Cholinergic receptor muscarinic 2	- Belongs to a larger family of G protein-coupled receptors. - Involves in neuronal excitability, synaptic plasticity and feedback regulation of acetylcholine (neurotransmitter and neuromodulator in the brain) release [272].

CREB1	cAMP responsive element binding protein 1	- Encodes a transcription factor that is a member of the leucine zipper family of DNA binding proteins. It promotes adult neurogenesis and mediates neurogenesis following neural damage, such as cerebral ischaemic stroke, by supporting survival of uninjured neurons or in the regeneration process [273]. - cAMP signaling pathway can transmit information initiated by neurotransmitters at the membrane to the cell nucleus, where it interacts with CREB to trigger processes that culminate in gene transcription [274].
CXCL1	C-X-C motif chemokine ligand 1	- The encoded protein is a secreted growth factor that signals through the G-protein coupled receptor, CXC receptor 2. - Regulates proliferation and differentiation of neuronal progenitor cells and serves as key regulator of neural progenitor proliferation [275].
CXCR4	C-X-C motif chemokine receptor 4	- CXCR4 expresses in various cancer, it is found to be a prognostic marker in various types of cancer. In addition, cancer stem cells also express CXCR4 [276].
DCX	Doublecortin	- Encodes a microtubule-associated protein that is essential for neuronal migration [277]. - Encodes a microtubule-associated protein, is essential for normal human brain development. Dcx/Dclk (doublecortin-like kinase)-efficient dissociated neurons show abnormal axon outgrowth with defects in axonal transport of synaptic vesicle proteins [278].
DLL1 (DELTA1)	Delta like canonical Notch ligand 1	- Notch signal is triggered by interaction with its ligand, the DSL family protein which includes Delta and Jagged/Serrate in vertebrates [279]. - Dll1 is presented on the surface of adherens junctions (AJs) formed at the apical termini of processes through interaction with MAGI1 to activate Notch signaling on neighboring cells in the developing central nervous system [280]. - Controls the rate of neurogenesis [281]. - Dll1 expression is oscillatory in neural stems cells. Defects of neural development happens when oscillation is dampened [282].
DRD2	Dopamine receptor D2	- DRD2 is a classical neurotransmitter [283] that controls movement, cognition, and motivational processes [284]. - Modulates GABA neuron migration from the basal forebrain to the cerebral cortex [285]. - Expressed in the developing rodent medial frontal cortex and influences development processes such as cell proliferation, migration, and neurite outgrowth. Unphysiological activation of dopamine receptors during brain development alters dendrite morphology and structural proteins that regulate the actin cytoskeleton [286]. - Modulates long-term changes in glutamatergic synaptic plasticity [287]. - This G-protein coupled receptor transmits dopamine signal, inhibits adenylyl cyclase activity, and decreases cAMP level [288].
DVL3	Dishevelled segment polarity protein 3	- Activates a key modulator of Wnt/β-catenin signaling pathway and plays a vital role in neural development [289]. - Regulates synaptic assembly and plasticity [290] and adult neurogenesis [291].

EFNB1	Ephrin B1	- Encodes a type I membrane protein that engages in cell signaling upon binding cognate Eph receptors, controls normal morphogenesis of the developing cortex. Ephrin B1 is required in apical progenitors (APs) to maintain their apical adhesion and it also controls cell-ECM adhesion by promoting apical localization of integrin β1 [292].
EGF	Epidermal growth factor	- Regulates cell proliferation and differentiation [293] and stimulates neurogenesis [294].
EP300	E1A binding protein p300	- Regulates the cell cycle through interactions with acetylation of proteins involved in cell-cycle progression [295]. - Modulates neurogenesis by upregulating EP300 [243]. - Regulates transcription via chromatin remodeling. It plays important roles in cell proliferation, transformation and differentiation [296].
ERBB2	Erb-b2 receptor tyrosine kinase 2	- Colocalizes in the membrane rafts with GM3, a ganglioside that serves regulatory roles in axonogenesis [297].
FGF2	Fibroblast growth factor 2	- Regulates the palmitoylation of neural cell adhesion molecule (NCAM) [298] which modulates adhesion between pre- and postsynaptic partners or by activation intracellular signaling cascades [299]. - Promotes cell proliferation and neurogenesis [300]. FGF2 promotes neuronal survival in vitro [301].
FLNA	Filamin A	- Encodes an actin-binding protein that crosslinks actin filaments and links actin filaments to membrane glycoproteins. FLNA regulates diverse aspects of cell development, including filopodia formation in non-neuronal cells, proliferation of cortical neural progenitors, and migration of diverse cell types including developing cortical neurons [302]. Loss of FLNA results in failed dampening of growth signals between neural progenitor cells and blood vessels, leading to excessive angiogenesis [303].
GDNF	Glial cell derived neurotrophic factor	- Prevent apoptosis of neurons [304]. - Increases proliferation and differentiation of progenitor cells during neurogenesis [305]. It also promotes the survival and differentiation of dopaminergic neurons in culture [306].
GPI (NLK)	Glucose-6-phosphate isomerase	- Acts as neurotrophic factor promoting neuron growth.
GRIN1	Glutamate ionotropic receptor NMDA type subunit 1	- Encodes the critical subunit of N-methyl-D-aspartate receptors that has critical role in synaptic transmission [307]. - Encodes the critical subunit of N-methyl-D-aspartate (NMDA) receptors that plays a key role in the plasticity of synapses [308].
HDAC4	Histone deacetylase 4	- Suppresses cell-cycle progression [309]. Cell proliferation was suppressed by knockout of HDAC4 [310]. - In responses to cerebral ischaemia, HDAC4 serves as an important HIF-VEGF signal-sensitive molecule to modulate angiogenesis, which promotes neurogenesis [311].
HES1	Hes family bHLH transcription factor 1	- Encodes a protein that belongs to the basic helix-loop-helix family of transcription factors. Expression of this gene is induced by the Notch signaling pathway that inhibits neuronal and muscle differentiation [312].

		- Expression of this gene is induced by the Notch signaling pathway. Level of Hes1 increased after ischaemia and decreased during the differentiation of neural progenitor cells [313].
HEY1	Hes related family bHLH transcription factor with YRPW motif 1	- Expression of this gene is induced by the Notch signaling pathway [313]. - Promotes maintenance of neural precursor cells [314].
HEY2	Hes related family bHLH transcription factor with YRPW motif 2	- Expression of this gene is induced by the Notch signaling pathway [313]. - Promotes maintenance of neural precursor cells [314].
HEYL	Hes related family bHLH transcription factor with YRPW motif-like	- Expression of this gene is induced by the Notch signaling pathway [313]. - Promotes neuronal differentiation of neural progenitor cells both in culture and in the embryonic brain in vivo [315].
IL10	Interleukin 10	- IL10 is a key immune regulator and acts as an anti-inflammatory cytokine. - Patients have significantly lowered IL-10 serum levels soon after the acute event, with a slight increase at the seventh day [237].
IL3	Interleukin 3	- Promotes cell growth [316] and possessed neurotrophic activity [317]. - The expression level of IL3 plays pivotal roles in the expansion and maintenance of the neural progenitor pool and the number of surviving neurons [318].
KMT2A (Mll1)	Lysine methyltransferase 2A	- Encodes a transcriptional coactivator that plays an essential role in neurogenesis by regulating neural progenitor proliferation and neuronal and glial differentiation [319].
LIF	LIF interleukin 6 family cytokine	- Encodes a protein that is a pleiotropic cytokine with roles in several different systems. It has profound effects on the survival and maintenance of motor neurons [111]. - Promotes neurogenesis [320], affects neuronal differentiation, and peripheral nerve regeneration [321].
MAP2	Microtubule associated protein 2	- Mainly expressed in neurons and involves in axonogenesis in developing cortical and hippocampal neuronal cultures [322].
MDK	Midkine	- Controls the cell cycle kinetics during neurogenesis [323]. Distinctive expression of midkine is found during the repair period of rat brain during neurogenesis [324]. Overexpression of MDK results in acceleration of the cell cycle [325]. - Promotes a variety of cellular functions leading to increased angiogenesis, proliferation, migration, and survival [326]. - Promotes migration of neuronal cells, accelerates neurite extension, and supports neuronal survival[362].
MEF2C	Myocyte enhancer factor 2C	- Encodes a member of the MADS box transcription enhancer factor 2 (MEF2) family of proteins that act as effectors of neurogenesis in the brain, with MEF2C the predominant isoform in developing cerebrocortex [327]. - In the CNS, transcription factor MEF2C induces neurogenesis. It is involved in neuronal apoptosis and synapse formation [328].
NDP	Norrin cystine knot growth factor NDP	- Encodes a secreted protein with a cystein-knot motif that activates the Wnt/beta-catenin pathway. - The Wnt/β-catenin pathway plays a vital role in neural development [289]. It regulates synaptic assembly and plasticity [290] and adult neurogenesis [291].
NEUROD1	Neuronal differentiation 1	- Encodes a member of the NeuroD family of basic helix-loop-helix (bHLH) transcription factors. Neurod1 is cell-intrinsically required for the survival and maturation of adult-born neurons. - Neurod1 is predominantly expressed in the nervous system late in development and is therefore more likely to be involved in terminal differentiation, neuronal maturation and survival [329].

NEUROG1	Neurogenin 1	- Encodes a neural-specific basic helix-loop-helix (bHLH) transcription factor that controls the timing of differentiation of early-born Cajal-Retzius neurons s and specifies the identities of later-born layer II/III neurons [330].
NEUROG2	Neurogenin 2	- Plays a prominent role in neurogenesis in the embryonic cortex and promotes neuron migration in the cortex [331]. - Encodes a neural-specific basic helix-loop-helix (bHLH) transcription factor that controls the timing of differentiation of early-born Cajal-Retzius neurons and specifies the identities of later-born layer II/III neurons [330].
NF1	Neurofibromin 1	- Regulates Ras/MAPK and cMAP signaling pathways which play acritical roles in controlling gene transcription during synaptic plasticity [332].
NOG	Noggin	- Encodes a polypeptide that binds and inactivates members of the transforming growth factor-beta (TGF-beta) superfamily signaling proteins which inhibits the differentiation of neocortical neurons [284].
NOTCH1	Notch receptor 1	- Encodes a member of the NOTCH family proteins. -Notch1 inhibits neurite outgrowth in postmitotic primary neurons [333]. - Regulates maintenance and self-renewal of neural stem cells [334]. - Activated form of Notch1 is expressed after ischaemia. Notch1 expression is downregulated during differentiation of neural progenitor cells [313].
NOTCH2	Notch receptor 2	- Induces growth arrest and apoptosis [335]. - Nothgenes (Notch1, Notch2, Notch3, and Notch4) encode receptors for a signally pathway that regulates neurogenesis [336]. - Maintains adult neural stem cell quiescence [334].
NRCAM	Neuronal cell adhesion molecule	- Involves in cell migration and synaptogenesis during embryonic and postnatal development [337]. - Functions of NrCAM are believed to include involvement in neurite outgrowth, axonal fasciculation and targeting, cell migration, and synaptogenesis during embryonic and postnatal development [337]. - NrCAM is a neuronal cell adhesion molecule of the L1 family of immunoglobulin super family. It plays a wide variety of roles in neural development, including cell proliferation and differentiation, axon growth and guidance, synapse formation, and the formation of the myelinated nerve structure [338]. - Affects growth of retinal ganglion cell axons [339].
NRG1 (HGL)	Neuregulin 1	- Encodes a protein that is a membrane glycoprotein that mediates cell-cell signaling. - Glial growth factor, promotes glia differentiation [340]. - Promotes proliferation of neuronal progenitor cells in vitro [341] and increases neurogenesis [342].
NRP1	Neuropilin 1	- Encodes one of two neuropilins, cell-surface glycoproteins that mediate cell adhesion by heterophilic molecular interactions. In all vertebrate species examined, the neuropilin protein is restricted to axons of particular neuron classes, and at stages when axon growth is active [343].
NRP2	Neuropilin 2	- Encodes one of two neuropilins, cell-surface glycoproteins that mediate cell adhesion by heterophilic molecular interactions. In all vertebrate species examined, the neuropilin protein is restricted to axons of particular neuron classes, and at stages when axon growth is active [343].
NTF3	Neurotrophin 3	- Encoded a protein that is a member of the neurotrophin family that controls differentiation of mammalian neurons [344].

OLIG2	Oligodendrocyte transcription factor 2	- Encodes a basic helix-loop-helix transcription factor that determines neuron versus glial fate determination and neuron subtype specification [345].
P2RX4	Purinergic receptor P2X4	- Encodes a protein family of purinoceptors for ATP. This is a ligand-gated ion channel with a function of high calcium permeability [346,347]. - P2RX4 is highly upregulated in the ischaemic brain [348].
P2RY1	Purinergic receptor P2Y1	- Encodes a protein family of G-protein coupled receptors. This gene functions as a receptor for extracellular ATP and ADP. In platelets binding to ADP leads to mobilization of intracellular calcium ions via activation of phospholipase C, a change in platelet shape [347,349]. - This receptor expressed in astrocytes may regulate the cytokine/chemokine response after ischaemia [350].
P2RY2	Purinergic receptor P2Y2	- Encodes a protein family of P2 receptors, which is activated by extracellular nucleotides and subdivided into P2X ligand-gated ion channels and P2Y G-protein coupled receptors [347,351]. - This gene could be related to the risk of ischaemic stroke in the Han Chinese population [352].
PAFAH1B1	Platelet activating factor acetylhydrolase 1b regulatory subunit 1	- Participates in neuronal migration. Mice with heterozygous deletion of Pafah1b1 exhibit many phenotypes of human lissencephaly, including defects in neuronal migration [353]. - Encodes microtubule-associated proteins (MAPs) which regulates neuronal differentiation [354]. - Mice with heterozygous deletion of Pafah1b1 produces a substantial enhancement of pre-synaptic glutamate transmission in hippocampus [355].
PARD3	Par-3 family cell polarity regulator	- Pard3 is a axonal transcript that guides local synthesis of proteins in the axons which participate in axonogenesis and axon guidance [356]. - Affects asymmetrical cell division and directs polarized cell growth [357]. During neocortical neurogenesis, the dynamic distribution of PARD3 in radial glial cells controls cell fate specification of the daughter cells [358].
Pax2	Paired box 2	- Encodes a homeobox and paired domain-containing protein that binds DNA and functions as a regulator of transcription. Pax-2 regulates dopaminergic neurogenesis by increasing the differentiation of cortical or ventral midbrain Nurr1 precursors into tyrosine hydroxylase-positive neurons [359].
PAX3	Paired box 3	- This gene is a member of the paired box (PAX) family of transcription factors. - Activation of PAX3 target genes is necessary for neuronal differentiation during neurogenesis in the opV placode [360]. - PAX3 inhibits constitutive apoptosis [361].
PAX6	Paired box 6	- Encodes a homeobox and paired domain-containing protein that binds DNA and functions as a regulator of transcription. Pax6 contributes to neurogenesis by patterning of the neural tube, migration of neurons, and formation of neural circuits [362].
POU3F3	POU class 3 homeobox 3 (BRN1)	- Encodes a POU-domain containing protein that functions as a transcription factor. It is implicated in diverse functions such as neurogenesis, cortical neural migration, and upper-layer production [363].
PROM1 (CD133)	Prominin 1	- CD133 has been used extensively as a marker for the identification of stem cells from normal and cancerous tissues [364].
PTN	Pleiotrophin	- Involves in cell growth, survival, migration and angiogenesis and play roles in neurogenesis [335]. PTN is up-regulated in injured cells [365].

		- Promotes angiogenesis, stimulates neurite outgrowth from cultured neurons, and induces cell migration [366]. PTN has neuroprotection effect [367].
RAC1	Rac family small GTPase 1	- Encodes a protein that is a GTPase which belongs to the RAS superfamily of small GTP-binding proteins. Rac1 is ubiquitously expressed and regulates cell adhesion, migration and differentiation in various cell types. -Depletion of Rac1 by short interference RNA leads to decreased cell-matrix adhesions and cell rounding in neuronal cells [368].
ROBO1	Roundabout guidance receptor 1	- Encodes a member of the immunoglobulin gene superfamily and encodes an integral membrane protein that regulates the development of major axon tracts and interneuron migration [369]. - Encodes an integral membrane protein of the immunoglobulin gene superfamily that functions in axon guidance and neuronal precursor cell migration. Binding of Slit to Robo receptor results in inactivation of the neural, calcium-dependent cell-cell adhesion molecule N-cadherin, providing a rapid epigenetic mechanism for integrating guidance and adhesion information [370].
RTN4	Reticulon 4 (Nogo)	- Encodes a family of reticulon that inhibits neurite outgrowth [371]. - Induces apoptosis and modulates neurogenesis by inhibiting regeneration of injured neurons in the central nervous system [372].
S100A6	S100 calcium binding protein A6	- Activates target proteins and influences cellular response along the calcium-signal-transduction pathway including the regulation of cell growth, proliferation, secretion, and exocytosis [373]. - Astrocytes located near impaired axons of motoneurons that were selectively programmed to die overexpress S100A6, a Ca^{2+}/Zn^{2+} binding protein able to translocate into the nucleus [186].
S100B	S100 calcium binding protein B	- Modulates long-term neuronal synaptic plasticity [187]. - Induces axonal extension and alterations [374].
SHH	Sonic hedgehog signaling molecule	- Increases proliferation of adult neural stem cells and plays a crucial role in neuroblasts migration [375]. - Shh is an antagonism of Wnt signaling. It facilitates midbrain floor plate neurogenesis [376].
SLIT2	Slit guidance ligand 2	- Encodes a member of the slit family of secreted glycoproteins, which are ligands for the Robo family of immunoglobulin receptors. Slit2 plays highly conserved roles in axon guidance and neuronal migration [377]. - Slit2 proteins are involved in guidance in axon and during neuronal migration [378]. - Binding of the secreted axon guidance cue Slit to its Robo receptor results in inactivation of the neural, calcium-dependent cell-cell adhesion molecule N-cadherin, providing a rapid epigenetic mechanism for integrating guidance and adhesion information [370].
SOD1	Superoxide dismutase 1	- The protein encoded by this gene binds copper and zinc ions and is responsible for destroying free superoxide radicals in the body. Mutant SOD1 has a multitude of pathogenic effects in neurons including neuroinflammation, excitotoxicity, axonal transport abnormalities [379].
SOX2	SRY-box 2	- Encodes a member of the SRY-related HMG-box (SOX) family of transcription factors involved in the regulation of embryonic development and in the determination of cell fate. Sox2 expression is essential for neural progenitor cell proliferation and differentiation the retina. It is also important for the differentiation of subsets of neurons [380].

SOX8	SRY-box 8	- Encodes a member of the SOX (SRY-related HMG-box) family of transcription factors involved in the regulation of embryonic development and in the determination of the cell fate. Mice lacking Sox8 showed substantial weight reduction and a transient delay in oligodendrocyte differentiation [381].
SPP1	Secreted phosphoprotein 1	- Encoded a protein that is involved in the attachment of osteoclasts to the mineralized bone matrix. - Stimulate neuroprotection and neurogenesis in the injured brain [382].
STAT3	Signal transducer and activator of transcription 3	- Encodes a protein that is a member of the STAT protein family. Suppression of Stat3 directly induces neurogenesis and inhibits astrogliogenesis in neural stem cells [383].
TGFB1	Transforming growth factor beta 1	- Encodes a secreted ligand of the TGF-beta superfamily of proteins that binds to TGF-beta receptors. - Stimulates cell proliferation or induces differentiation. Loss of TGFB1 leads to increased neuronal cell death [384]. - Required for late-stage neuronal development, maturation, and survival [385].
TH	Tyrosine hydroxylase	- Encoded a protein that is involved in the conversion of tyrosine to dopamine. - Promotes dopaminergic neurogenesis [386].
TNF	Tumor necrosis factor	- Encodes a multifunctional proinflammatory cytokine that belongs to the tumor necrosis factor (TNF) superfamily. - Increases production of proinflammatory molecules and inhibits neuronal survival and differentiation [387].
TNR	Tenascin R	- Encodes a member of the tenascin family of extracellular matrix glycoproteins that is restricted to the central nervous system. Mammalian TNR is adhesive for astrocytes and antiadhesive for various CNS neurons, It causes the detachment of neuronal cells from and inhibits axonal outgrowth into TNR-containing substrates in vitro by its interaction with the neuronal protein F3/11 [388].
VEGFA	Vascular endothelial growth factor A	- Protects cells from apoptosis [323] and promotes neurogenesis, neuronal migration, neuronal survival and axon guidance [324]. - Guides angiogenesis [344].

References

1 Herzog, R., Zendedel, A., Lammerding, L., Beyer, C. & Slowik, A. Impact of 17beta-estradiol and progesterone on inflammatory and apoptotic microRNA expression after ischemia in a rat model. *J. Steroid Biochem. Mol. Biol.* **167**, 126-134 (2017).

2 Yang, B.-y. *et al.* PSMB8 regulates glioma cell migration, proliferation, and apoptosis through modulating ERK1/2 and PI3K/AKT signaling pathways. *Biomed. Pharmacother.* **100**, 205-212 (2018).

3 Chen, X. *et al.* Inhibition of immunoproteasome reduces infarction volume and attenuates inflammatory reaction in a rat model of ischemic stroke. *Cell Death Dis.* **6**, e1626 (2015).

4 O'Reilly, A. M., Currie, R. W. & Clarke, D. B. HspB1 (Hsp 27) expression and neuroprotection in the retina. *Mol. Neurobiol.* **42**, 124-132 (2010).

5 Liu, B., Li, J., Li, L., Yu, L. & Li, C. Electrical stimulation of cerebellar fastigial nucleus promotes the expression of growth arrest and DNA damage inducible gene β and motor function recovery in cerebral ischemia/reperfusion rats. *Neurosci. Lett.* **520**, 110-114 (2012).

6 Liu, B. *et al.* Gadd45b is a novel mediator of neuronal apoptosis in ischemic stroke. *Int. J. Biol. Sci.* **11**, 353-360 (2015).

7 Xingyong, C. *et al.* Upregulation of myeloid cell leukemia-1 potentially modulates beclin-1-dependent autophagy in ischemic stroke in rats. *BMC Neurosci.* **14**, 56-64 (2013).

8 Saito, A., Hayashi, T., Okuno, S., Ferrand-Drake, M. & Chan, P. H. Interaction between XIAP and Smac/DIABLO in the mouse brain after transient focal cerebral ischemia. *J. Cerebr. Blood F. Met.* **23**, 1010-1019 (2003).

9 Büttner, F. *et al.* Genomic response of the rat brain to global ischemia and reperfusion. *Brain Res.* **1252**, 1-14 (2009).

10 Wang, X., Li, R., Wang, X., Fu, Q. & Ma, S. Umbelliferone ameliorates cerebral ischemia–reperfusion injury via upregulating the PPAR gamma expression and suppressing TXNIP/NLRP3 inflammasome. *Neurosci. Lett.* **600**, 182-187 (2015).

11 Pulliam, J. V. *et al.* Computational identification of conserved transcription factor binding sites upstream of genes induced in rat brain by transient focal ischemic stroke. *Brain Res.* **1495**, 76-85 (2013).

12 Muhammad, S., Bierhaus, A. & Schwaninger, M. Reactive oxygen species in diabetes-induced vascular damage, stroke, and Alzheimer's disease. *J. Alzheimers Dis.* **16**, 775-785 (2009).

13 Hogarth, P. M. & Pietersz, G. A. Fc receptor-targeted therapies for the treatment of inflammation, cancer and beyond. *Nat. Rev. Drug Discov.* **11**, 311-331 (2012).

14 Walker, D. G., Link, J., Lue, L. F., Dalsing-Hernandez, J. E. & Boyes, B. E. Gene expression changes by amyloid β peptide-stimulated human postmortem brain microglia identify activation of multiple inflammatory processes. *J. Leukocyte Biol.* **79**, 596-610 (2006).

15 Maino, B. *et al.* The trophic effect of nerve growth factor in primary cultures of rat hippocampal neurons is associated to an anti-inflammatory and immunosuppressive transcriptional program. *J. Cell Physiol.* **233**, 7178-7187 (2018).

16 Mishra, A. & Brinton, R. D. Inflammation: Bridging Age, Menopause and APOEε4 Genotype to Alzheimer's Disease. *Front. Aging Neurosci.* **10** (2018).

17 Zhu, W. *et al.* Postischemic IGF-1 gene transfer promotes neurovascular regeneration after experimental stroke. *J. Cerebr. Blood F. Met.* **29**, 1528-1537 (2009).

18 Bake, S., Selvamani, A., Cherry, J. & Sohrabji, F. Blood brain barrier and neuroinflammation are critical targets of IGF-1-mediated neuroprotection in stroke for middle-aged female rats. *Plos One* **9**, e91427 (2014).

19 Shibuya, M. Brain angiogenesis in developmental and pathological processes: therapeutic aspects of vascular endothelial growth factor. *FEBS J.* **276**, 4636-4643 (2009).

20 Mackenzie, F. & Ruhrberg, C. Diverse roles for VEGF-A in the nervous system. *Development* **139**, 1371-1380 (2012).

21 Greenberg, D. A. & Jin, K. Vascular endothelial growth factors (VEGFs) and stroke. *Cell Mol. Life Sci.* **70**, 1753-1761 (2013).

22 Cao, Y. *et al.* Vascular endothelial growth factor C induces angiogenesis in vivo. *Proc. Natl. Acad. Sci.* **95**, 14389-14394 (1998).

23 Shin, Y.-J. *et al.* Enhanced expression of vascular endothelial growth factor receptor-3 in the subventricular zone of stroke-lesioned rats. *Neurosci. Lett.* **469**, 194-198 (2010).

24 Ren, T. *et al.* Apurinic/apyrimidinic endonuclease 1 induced upregulation of fibroblast growth factor 2 and its receptor 3 induces angiogenesis in human osteosarcoma cells. *Cancer Sci.* **105**, 186-194 (2014).

25 Kang, S. S. *et al.* Endogenous CNTF mediates stroke-induced adult CNS neurogenesis in mice. *Neurobiol. Dis.* **49**, 68-78 (2013).

26 Ruocco, A. *et al.* A transforming growth factor-β antagonist unmasks the neuroprotective role of this endogenous cytokine in excitotoxic and ischemic brain injury. *J. Cerebr. Blood F. Met.* **19**, 1345-1353 (1999).

27 Vallon, M., Chang, J., Zhang, H. & Kuo, C. J. Developmental and pathological angiogenesis in the central nervous system. *Cell Mol. Life Sci.* **71**, 3489-3506 (2014).

28 Krupinski, J., Kumar, P., Kumar, S. & Kaluza, J. Increased expression of TGF-β1 in brain tissue after ischemic stroke in humans. *Stroke* **27**, 852-857 (1996).

29 Poulsen, K. *et al.* TGFβ2 and TGFβ3 are potent survival factors for midbrain dopaminergic neurons. *Neuron* **13**, 1245-1252 (1994).

30 Li, S. *et al.* An age-related sprouting transcriptome provides molecular control of axonal sprouting after stroke. *Nat. Neurosci.* **13**, 1496-1504 (2010).
31 Won, S. J. *et al.* Reelin-deficient mice show impaired neurogenesis and increased stroke size. *Exp. Neurol.* **198**, 250-259 (2006).
32 Tonchev, A., Yamashima, T., Guo, J., Chaldakov, G. & Takakura, N. Expression of angiogenic and neurotrophic factors in the progenitor cell niche of adult monkey subventricular zone. *Neuroscience* **144**, 1425-1435 (2007).
33 Sarabi, A., Chang, C., Wang, Y., Hoffer, B. & Morales, M. Time course study of GFRα-1 expression in an animal model of stroke. *Exp. Neurol.* **170**, 283-289 (2001).
34 Kawahara, N. *et al.* The gene for heparin-binding epidermal growth factor-like growth factor is stress-inducible: its role in cerebral ischemia. *J. Cerebr. Blood F. Met.* **19**, 307-320 (1999).
35 Sugiura, S. *et al.* Adenovirus-mediated gene transfer of heparin-binding epidermal growth factor-like growth factor enhances neurogenesis and angiogenesis after focal cerebral ischemia in rats. *Stroke* **36**, 859-864 (2005).
36 Tokunaga, N. *et al.* Adrenomedullin gene transfer induces therapeutic angiogenesis in a rabbit model of chronic hind limb ischemia: benefits of a novel nonviral vector, gelatin. *Circulation* **109**, 526-531 (2004).
37 Kato, H., Shichiri, M., Marumo, F. & Hirata, Y. Adrenomedullin as an autocrine/paracrine apoptosis survival factor for rat endothelial cells. *Endocrinology* **138**, 2615-2620 (1997).
38 Xia, C.-F., Yin, H., Borlongan, C. V., Chao, J. & Chao, L. Postischemic infusion of adrenomedullin protects against ischemic stroke by inhibiting apoptosis and promoting angiogenesis. *Exp. Neurol.* **197**, 521-530 (2006).
39 Fernández-López, D. *et al.* Blood–brain barrier permeability is increased after acute adult stroke but not neonatal stroke in the rat. *J. Neurosci.* **32**, 9588-9600 (2012).
40 Nagahara, A. H. & Tuszynski, M. H. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. *Nat. Rev. Drug Discov.* **10**, 209-219 (2011).
41 Fouda, A. Y. *et al.* Brain-derived neurotrophic factor knockdown blocks the angiogenic and protective effects of angiotensin modulation after experimental stroke. *Mol. Neurobiol.* **54**, 661-670 (2017).
42 Kalus, I. *et al.* Sulf1 and Sulf2 differentially modulate heparan sulfate proteoglycan sulfation during postnatal cerebellum development: evidence for neuroprotective and neurite outgrowth promoting functions. *Plos One* **10**, e0139853 (2015).
43 Verma, A. *et al.* Endothelial cell-specific chemotaxis receptor (ecscr) promotes angioblast migration during vasculogenesis and enhances VEGF receptor sensitivity. *Blood* **115**, 4614-4622 (2010).
44 Ondrovics, M., Hoelbl-Kovacic, A. & Fux, D. A. Opioids: modulators of angiogenesis in wound healing and cancer. *Oncotarget* **8**, 25783-25796 (2017).
45 Yang, M., Guo, M., Hu, Y. & Jiang, Y. Scube regulates synovial angiogenesis-related signaling. *Med. Hypotheses* **81**, 948-953 (2013).
46 Samanta, J., Alden, T., Gobeske, K., Kan, L. & Kessler, J. A. Noggin protects against ischemic brain injury in rodents. *Stroke* **41**, 357-362 (2010).
47 Sun, J. & Nan, G. The mitogen-activated protein kinase (MAPK) signaling pathway as a discovery target in stroke. *J. Mol. Neurosci.* **59**, 90-98 (2016).
48 Lakhan, S. E., Kirchgessner, A. & Hofer, M. Inflammatory mechanisms in ischemic stroke: therapeutic approaches. *J. Transl. Med.* **7**, 1-11 (2009).
49 Vidale, S., Consoli, A., Arnaboldi, M. & Consoli, D. Postischemic inflammation in acute stroke. *J. Clin. Neurol.* **13**, 1-9 (2017).
50 Lalancette-Hébert, M. *et al.* Galectin-3 is required for resident microglia activation and proliferation in response to ischemic injury. *J. Neurosci.* **32**, 10383-10395 (2012).
51 Netea, M. G. *et al.* IL-32 synergizes with nucleotide oligomerization domain (NOD) 1 and NOD2 ligands for IL-1β and IL-6 production through a caspase 1-dependent mechanism. *Proc. Natl. Acad. Sci.* **102**, 16309-16314 (2005).
52 Zhang, Y., Park, T. S. & Gidday, J. M. Hypoxic preconditioning protects human brain endothelium from ischemic apoptosis by Akt-dependent survivin activation. *Am. J. Physiol.-Heart C.* (2007).
53 Wacker, B. K., Park, T. S. & Gidday, J. M. Hypoxic preconditioning-induced cerebral ischemic tolerance: role of microvascular sphingosine kinase 2. *Stroke* **40**, 3342-3348 (2009).
54 Brait, V. H. *et al.* Chemokine-related gene expression in the brain following ischemic stroke: no role for CXCR2 in outcome. *Brain Res.* **1372**, 169-179 (2011).
55 Seifert, H. A. *et al.* Pro-inflammatory interferon gamma signaling is directly associated with stroke induced neurodegeneration. *J. Neuroimmune Pharm.* **9**, 679-689 (2014).
56 Rodriguez-Grande, B. *et al.* The acute-phase protein PTX3 is an essential mediator of glial scar formation and resolution of brain edema after ischemic injury. *J. Cerebr. Blood F. Met.* **34**, 480-488 (2014).
57 Landi, S. *et al.* Polymorphisms within inflammatory genes and colorectal cancer. *J. Negat. Results Biomed.* **5**, 15-19 (2006).
58 Tanriverdi, T. *et al.* Lack of association between the IL1A gene (-889) polymorphism and outcome after head injury. *Surg. Neurol.* **65**, 7-10 (2006).
59 Nakase, T., Yamazaki, T., Ogura, N., Suzuki, A. & Nagata, K. The impact of inflammation on the pathogenesis and prognosis of ischemic stroke. *J. Neurol. Sci.* **271**, 104-109 (2008).

60 Cheung, T. C. *et al.* Unconventional ligand activation of herpesvirus entry mediator signals cell survival. *Proc. Natl. Acad. Sci.* **106**, 6244-6249 (2009).
61 Yang, D. *et al.* Transcriptomic analysis of mild hypothermia-dependent alterations during endothelial reperfusion injury. *Cell. Physiol. Biochem.* **25**, 605-614 (2010).
62 Bruce, A. J. *et al.* Altered neuronal and microglial responses to excitotoxic and ischemic brain injury in mice lacking TNF receptors. *Nat. Med.* **2**, 788-794 (1996).
63 Abcouwer, S. F. *et al.* Minocycline prevents retinal inflammation and vascular permeability following ischemia-reperfusion injury. *J. Neuroinflamm.* **10**, 1-14 (2013).
64 Krupinski, J., Kaluza, J., Kumar, P., Kumar, S. & Wang, J. M. Role of angiogenesis in patients with cerebral ischemic stroke. *Stroke* **25**, 1794-1798 (1994).
65 Thirumangalakudi, L., Samany, P. G., Owoso, A., Wiskar, B. & Grammas, P. Angiogenic proteins are expressed by brain blood vessels in Alzheimer's disease. *J. Alzheimers Dis.* **10**, 111-118 (2006).
66 Liu, X. S. *et al.* Comparison of in vivo and in vitro gene expression profiles in subventricular zone neural progenitor cells from the adult mouse after middle cerebral artery occlusion. *Neuroscience* **146**, 1053-1061 (2007).
67 Jin, G. *et al.* CD47 gene knockout protects against transient focal cerebral ischemia in mice. *Exp. Neurol.* **217**, 165-170 (2009).
68 Stamova, B. *et al.* Gene expression in peripheral immune cells following cardioembolic stroke is sexually dimorphic. *Plos One* **9**, e102550 (2014).
69 Khan, A. *et al.* Transcriptomic analysis reveals differential activation of microglial genes after ischemic stroke in mice. *Neuroscience* **348**, 212-227 (2017).
70 Baeten, K. M. & Akassoglou, K. Extracellular matrix and matrix receptors in blood–brain barrier formation and stroke. *De. Neurobiol.* **71**, 1018-1039 (2011).
71 Castellanos, M. *et al.* Plasma cellular-fibronectin concentration predicts hemorrhagic transformation after thrombolytic therapy in acute ischemic stroke. *Stroke* **35**, 1671-1676 (2004).
72 Hamann, G. F., Okada, Y. & del Zoppo, G. J. Hemorrhagic transformation and microvascular integrity during focal cerebral ischemia/reperfusion. *J. Cerebr. Blood F. Met.* **16**, 1373-1378 (1996).
73 Fukuda, S. *et al.* Focal cerebral ischemia induces active proteases that degrade microvascular matrix. *Stroke* **35**, 998-1004 (2004).
74 Volonghi, I. *et al.* Role of COL4A1 in basement-membrane integrity and cerebral small-vessel disease. The COL4A1 stroke syndrome. *Curr. Med. Chem.* **17**, 1317-1324 (2010).
75 Jeanne, M. *et al.* COL4A2 mutations impair COL4A1 and COL4A2 secretion and cause hemorrhagic stroke. *Am. J. Hum. Genet.* **90**, 91-101 (2012).
76 Sapojnikova, N. *et al.* Correlation between MMP-9 and extracellular cytokine HMGB1 in prediction of human ischemic stroke outcome. *BBA-Mol. Basis Dis.* **1842**, 1379-1384 (2014).
77 Taylor, R. A. & Sansing, L. H. Microglial responses after ischemic stroke and intracerebral hemorrhage. *Clin. Dev. Immunol.* **2013** (2013).
78 Clark, A. W., Krekoski, C. A., Bou, S.-S., Chapman, K. R. & Edwards, D. R. Increased gelatinase A (MMP-2) and gelatinase B (MMP-9) activities in human brain after focal ischemia. *Neurosci. Lett.* **238**, 53-56 (1997).
79 Romanic, A. M., White, R. F., Arleth, A. J., Ohlstein, E. H. & Barone, F. C. Matrix metalloproteinase expression increases after cerebral focal ischemia in rats. *Stroke* **29**, 1020-1030 (1998).
80 Hajjar, K. A. & Acharya, S. S. Annexin II and regulation of cell surface fibrinolysis. *Ann. Ny. Acad. Sci.* **902**, 265-271 (2000).
81 Cha, J.-H. *et al.* AKAP12 mediates barrier functions of fibrotic scars during CNS repair. *Plos One* **9**, e94695 (2014).
82 Yang, Q. *et al.* Blocking epidermal growth factor receptor attenuates reactive astrogliosis through inhibiting cell cycle progression and protects against ischemic brain injury in rats. *J. Neurochem.* **119**, 644-653 (2011).
83 Nieto-Sampedro, M., Gómez-Pinilla, F., Knauer, D. J. & Broderick, J. T. Epidermal growth factor receptor immunoreactivity in rat brain astrocytes. Response to injury. *Neurosci. Lett.* **91**, 276-282 (1988).
84 Shiba, M. *et al.* Imatinib mesylate prevents cerebral vasospasm after subarachnoid hemorrhage via inhibiting tenascin-C expression in rats. *Neurobiol. Dis.* **46**, 172-179 (2012).
85 Hertel, M., Tretter, Y., Alzheimer, C. & Werner, S. Connective tissue growth factor: a novel player in tissue reorganization after brain injury? *Eur. J. Neurosci.* **12**, 376-380 (2000).
86 Dahlstrand, J., Zimmerman, L. B., McKay, R. D. & Lendahl, U. Characterization of the human nestin gene reveals a close evolutionary relationship to neurofilaments. *J. Cell Sci.* **103 (Pt 2)**, 589-597 (1992).
87 Li, Y. & Chopp, M. Temporal profile of nestin expression after focal cerebral ischemia in adult rat. *Brain Res.* **838**, 1-10 (1999).
88 Miltenberger-Miltenyi, G. *et al.* Clinical and electrophysiological features in Charcot-Marie-Tooth disease with mutations in the NEFL gene. *Arch. Neurol.* **64**, 966-970 (2007).
89 Tiedt, S. *et al.* Serum neurofilament light: A biomarker of neuroaxonal injury after ischemic stroke. *Neurology* **91**, 1338-1347 (2018).
90 Chen, L. T., Gilman, A. G. & Kozasa, T. A candidate target for G protein action in brain. *J. Biol. Chem.* **274**, 26931-26938 (1999).
91 GrandPre, T., Nakamura, F., Vartanian, T. & Strittmatter, S. M. Identification of the Nogo inhibitor of axon regeneration as a Reticulon protein. *Nature* **403**, 439-444 (2000).

92 Yu, J. *et al.* Reticulon 4B (Nogo-B) is necessary for macrophage infiltration and tissue repair. *P. Natl. Acad. Sci. USA* **106**, 17511-17516 (2009).
93 Nielander, H. B. *et al.* Structure of the human gene for the neural phosphoprotein B-50 (GAP-43). *Brain Res. Mol. Brain Res.* **19**, 293-302 (1993).
94 Zhang, S., Xia, Y. Y., Lim, H. C., Tang, F. R. & Feng, Z. W. NCAM-mediated locomotor recovery from spinal cord contusion injury involves neuroprotection, axon regeneration, and synaptogenesis. *Neurochem. Int.* **56**, 919-929 (2010).
95 Stroemer, R. P., Kent, T. A. & Hulsebosch, C. E. Acute increase in expression of growth associated protein GAP-43 following cortical ischemia in rat. *Neurosci. Lett.* **162**, 51-54 (1993).
96 Toth, A. B. *et al.* Synapse maturation by activity-dependent ectodomain shedding of SIRPα. *Nat. Neurosci.* **16**, 1417-1425 (2013).
97 Wang, L. *et al.* SHPS-1 deficiency induces robust neuroprotection against experimental stroke by attenuating oxidative stress. *J. Neurochem.* **122**, 834-843 (2012).
98 Bruzzone, R., Hormuzdi, S. G., Barbe, M. T., Herb, A. & Monyer, H. Pannexins, a family of gap junction proteins expressed in brain. *Proceedings of the National Academy of Sciences of the United States of America* **100**, 13644-13649 (2003).
99 Ardiles, A. O. *et al.* Pannexin 1 regulates bidirectional hippocampal synaptic plasticity in adult mice. *Front Cell Neurosci.* **8** (2014).
100 Weilinger, N. L., Tang, P. L. & Thompson, R. J. Anoxia-induced NMDA receptor activation opens pannexin channels via Src family kinases. *J. Neurosci.***32**, 12579-12588 (2012).
101 Walsh, F. S. *et al.* N-cadherin gene maps to human chromosome 18 and is not linked to the E-cadherin gene. *J. Neurochem.* **55**, 805-812 (1990).
102 McGregor, N., Lochner, C., Stein, D. & Hemmings, S. Polymorphisms within the neuronal cadherin (CDH2) gene are associated with obsessive-compulsive disorder (OCD) in a South African cohort. *Metab. Brain Dis.* **31**, 191-196 (2016).
103 Costain, W. J. *et al.* Cerebral ischemia causes dysregulation of synaptic adhesion in mouse synaptosomes. *J. Cerebr Blood F. Met.* **28**, 99-110 (2008).
104 Risher, W. C. & Eroglu, C. Thrombospondins as key regulators of synaptogenesis in the central nervous system. *Matrix Biol.* **31**, 170-177 (2012).
105 Liauw, J. *et al.* Thrombospondins 1 and 2 are necessary for synaptic plasticity and functional recovery after stroke. *J. Cerebr. Blood F. Met.* **28**, 1722-1732 (2008).
106 Sudhof, T. C. The structure of the human synapsin I gene and protein. *J. Biol. Chem.* **265**, 7849-7852 (1990).
107 Bernabeu, R. & Sharp, F. R. NMDA and AMPA/kainate glutamate receptors modulate dentate neurogenesis and CA3 synapsin-I in normal and ischemic hippocampus. *J. Cerebr Blood F. Met.* **20**, 1669-1680 (2000).
108 Mody, I. & Heinemann, U. NMDA receptors of dentate gyrus granule cells participate in synaptic transmission following kindling. *Nature* **326**, 701-704 (1987).
109 Aarts, M. *et al.* Treatment of ischemic brain damage by perturbing NMDA receptor-PSD-95 protein interactions. *Science* **298**, 846-850 (2002).
110 Südhof, T. C. Neuroligins and neurexins link synaptic function to cognitive disease. *Nature* **455**, 903-911 (2008).
111 Li, M., Sendtner, M. & Smith, A. Essential function of LIF receptor in motor neurons. *Nature* **378-727**, 724 (1995).
112 Wang, L. *et al.* The Notch pathway mediates expansion of a progenitor pool and neuronal differentiation in adult neural progenitor cells after stroke. *Neuroscience* **158**, 1356-1363 (2009).
113 Alder, J. *et al.* Brain-derived neurotrophic factor-induced gene expression reveals novel actions of VGF in hippocampal synaptic plasticity. *J. Neurosci.* **23**, 10800-10808 (2003).
114 Barria, A. & Malinow, R. NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. *Neuron* **48**, 289-301 (2005).
115 Pines, G. *et al.* Cloning and expression of a rat brain L-glutamate transporter. *Nature* **360**, 464-467 (1992).
116 Rao, V. L. *et al.* Antisense knockdown of the glial glutamate transporter GLT-1, but not the neuronal glutamate transporter EAAC1, exacerbates transient focal cerebral ischemia-induced neuronal damage in rat brain. *J. Neurosci.* **21**, 1876-1883 (2001).
117 Zhang, M. *et al.* p38 MAPK Participates in the Mediation of GLT-1 Up-regulation During the Induction of Brain Ischemic Tolerance by Cerebral Ischemic Preconditioning. *Mol. Neurobiol.* **54**, 58-71 (2017).
118 Pin, J. P. & Bockaert, J. Get receptive to metabotropic glutamate receptors. *Curr. Opin. Neurol.* **5**, 342-349 (1995).
119 Wei, X., Miou, Z. & Baudry, M. Neuroprotection by cell permeable TAT-mGluR1 peptide in ischemia: synergy between carrier and cargo sequences. *Neuroscientist* **14**, 409-414 (2008).
120 Yamasaki, T. *et al.* Dynamic Changes in Striatal mGluR1 But Not mGluR5 during Pathological Progression of Parkinson's Disease in Human Alpha-Synuclein A53T Transgenic Rats: A Multi-PET Imaging Study. *J. Neurosci.* **36**, 375-384 (2016).
121 Oliver, C. N. *et al.* Oxidative damage to brain proteins, loss of glutamine synthetase activity, and production of free radicals during ischemia/reperfusion-induced injury to gerbil brain. *P. Natl. Acad. Sci. USA* **87**, 5144-5147 (1990).
122 Gorovits, R., Avidan, N., Avisar, N., Shaked, I. & Vardimon, L. Glutamine synthetase protects against neuronal degeneration in injured retinal tissue. *P. Natl. Acad. Sci. USA* **94**, 7024-7029 (1997).

123 Archer, B. T., 3rd, Ozcelik, T., Jahn, R., Francke, U. & Sudhof, T. C. Structures and chromosomal localizations of two human genes encoding synaptobrevins 1 and 2. *J. Biol. Chem.* **265**, 17267-17273 (1990).
124 Bacci, A. *et al.* Chronic blockade of glutamate receptors enhances presynaptic release and downregulates the interaction between synaptophysin-synaptobrevin-vesicle-associated membrane protein 2. *J. Neurosci.* **21**, 6588-6596 (2001).
125 Burgess, D. L., Davis, C. F., Gefrides, L. A. & Noebels, J. L. Identification of three novel Ca(2+) channel gamma subunit genes reveals molecular diversification by tandem and chromosome duplication. *Genome Res.* **9**, 1204-1213 (1999).
126 Osei, Y. D. & Churchich, J. E. Screening and sequence determination of a cDNA encoding the human brain 4-aminobutyrate aminotransferase. *Gene* **155**, 185-187 (1995).
127 Miller, P. S. & Aricescu, A. R. Crystal structure of a human GABAA receptor. *Nature* **512**, 270-275 (2014).
128 Lee, J. M., Grabb, M. C., Zipfel, G. J. & Choi, D. W. Brain tissue responses to ischemia. *J. Clin. Invest.* **106**, 723-731 (2000).
129 Abbott, N. J., Patabendige, A. A., Dolman, D. E., Yusof, S. R. & Begley, D. J. Structure and function of the blood–brain barrier. *Neurobiol. Dis.* **37**, 13-25 (2010).
130 Abdullahi, W., Tripathi, D. & Ronaldson, P. T. Blood-brain barrier dysfunction in ischemic stroke: targeting tight junctions and transporters for vascular protection. *Am. J. Physiol.-Cell Ph.* (2018).
131 Stamatovic, S. M., Johnson, A. M., Keep, R. F. & Andjelkovic, A. V. Junctional proteins of the blood-brain barrier: new insights into function and dysfunction. *Tissue barriers* **4**, e1154641 (2016).
132 Siushansian, R., Bechberger, J. F., Cechetto, D. F., Hachinski, V. C. & Naus, C. C. Connexin43 null mutation increases infarct size after stroke. *J. Comp. Neurol.* **440**, 387-394 (2001).
133 Jiao, H., Wang, Z., Liu, Y., Wang, P. & Xue, Y. Specific role of tight junction proteins claudin-5, occludin, and ZO-1 of the blood–brain barrier in a focal cerebral ischemic insult. *J. Mol. Neurosci.* **44**, 130-139 (2011).
134 Yang, B. *et al.* Increase in angiotensin II type 1 receptor expression immediately after ischemia-reperfusion in isolated rat hearts. *Circulation* **96**, 922-926 (1997).
135 Ekelund, U., Adner, M., Edvinsson, L. & Mellander, S. Effects of selective ETB-receptor stimulation on arterial, venous and capillary functions in cat skeletal muscle. *Brit. J. Pharmacol.* **112**, 887-894 (1994).
136 Stenman, E. *et al.* Cerebral ischemia upregulates vascular endothelin ETB receptors in rat. *Stroke* **33**, 2311-2316 (2002).
137 Wu, X. *et al.* Increased expression of actin filament-stabilizing protein tropomyosin after rat traumatic brain injury. *J. Mol. Histol.* **44**, 37-45 (2013).
138 Zhang, H.-F. *et al.* Inhibition of myosin light chain kinase reduces NADPH oxidase-mediated oxidative injury in rat brain following cerebral ischemia/reperfusion. *N-S Arch. Pharmacol.* **388**, 953-963 (2015).
139 DeLisser, H. M. *et al.* Involvement of endothelial PECAM-1/CD31 in angiogenesis. *Am. J. Pathol.* **151**, 671 (1997).
140 Newman, P. J. The biology of PECAM-1. *J. Clin. Invest.* **99**, 3-8 (1997).
141 Marti, H. J. *et al.* Hypoxia-induced vascular endothelial growth factor expression precedes neovascularization after cerebral ischemia. *Am. J. Pathol.* **156**, 965-976 (2000).
142 Lacotte, S., Brun, S., Muller, S. & Dumortier, H. CXCR3, inflammation, and autoimmune diseases. *Ann. Ny. Acad. Sci.* **1173**, 310-317 (2009).
143 Sobel, R. A., Mitchell, M. E. & Fondren, G. Intercellular adhesion molecule-1 (ICAM-1) in cellular immune reactions in the human central nervous system. *Am. J. Pathol.* **136**, 1309 (1990).
144 Lindsberg, P. J., Carpe´ n, O., Paetau, A., Karjalainen-Lindsberg, M.-L. & Kaste, M. Endothelial ICAM-1 expression associated with inflammatory cell response in human ischemic stroke. *Circulation* **94**, 939-945 (1996).
145 Puré, E. & Cuff, C. A. A crucial role for CD44 in inflammation. *Trends Mol. Med.* **7**, 213-221 (2001).
146 Wang, X. *et al.* CD44 deficiency in mice protects brain from cerebral ischemia injury. *J. Neurochem.* **83**, 1172-1179 (2002).
147 Crisan, M. *et al.* A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell stem cell* **3**, 301-313 (2008).
148 Ferland-McCollough, D., Slater, S., Richard, J., Reni, C. & Mangialardi, G. Pericytes, an overlooked player in vascular pathobiology. *Pharmacol. Ther.* **171**, 30-42 (2017).
149 Murfee, W. L., Rehorn, M. R., Peirce, S. M. & Skalak, T. C. Perivascular cells along venules upregulate NG2 expression during microvascular remodeling. *Microcirculation* **13**, 261-273 (2006).
150 Arimura, K. *et al.* PDGF receptor beta signaling in pericytes following ischemic brain injury. *Curr. Neurovasc. Res.* **9**, 1-9 (2012).
151 Sosnoski, D. M. *et al.* Chromosomal localization of the genes for the vitronectin and fibronectin receptors alpha subunits and for platelet glycoproteins IIb and IIIa. *J. Clin. Invest.* **81**, 1993-1998 (1988).
152 Lemos, D. R. *et al.* Maintenance of vascular integrity by pericytes is essential for normal kidney function. *Am. J. Physiol. Renal Physiol.* **311**, 1230-1242 (2016).
153 Claeys, K. G. *et al.* Differential involvement of sarcomeric proteins in myofibrillar myopathies: a morphological and immunohistochemical study. *Acta neuropathol.* **7**, 293-307 (2009).
154 Nehls, V. & Drenckhahn, D. The versatility of microvascular pericytes: from mesenchyme to smooth muscle? *Histochemistry* **99**, 1-12 (1993).

155 Bondjers, C. *et al.* Transcription profiling of platelet-derived growth factor-B-deficient mouse embryos identifies RGS5 as a novel marker for pericytes and vascular smooth muscle cells. *Am. J. Clin. Pathol.* **162**, 721-729 (2003).
156 Guclu, M. *et al.* The effects of melatonin on intestinal adaptation in a rat model of short bowel syndrome. *Eur. J. Pediatr. Surg.* **24**, 150-157 (2014).
157 Ozen, I. *et al.* Loss of Regulator of G-Protein Signaling 5 Leads to Neurovascular Protection in Stroke. *Stroke* **49**, 2182-2190 (2018).
158 Hess, A. R. *et al.* Molecular regulation of tumor cell vasculogenic mimicry by tyrosine phosphorylation: role of epithelial cell kinase (Eck/EphA2). *Cancer Res.* **61**, 3250-3255 (2001).
159 Thundyil, J. *et al.* Evidence that the EphA2 receptor exacerbates ischemic brain injury. *PloS one* **8**, e53528 (2013).
160 Bandopadhyay, R. *et al.* Contractile proteins in pericytes at the blood-brain and blood-retinal barriers. *J. Neurocytol.* **30**, 35-44 (2001).
161 Dubrac, A. *et al.* NCK-dependent pericyte migration promotes pathological neovascularization in ischemic retinopathy. *Nat. Commun.* **9**, 3463 (2018).
162 Christian, S. *et al.* Molecular cloning and characterization of endosialin, a C-type lectin-like cell surface receptor of tumor endothelium. *J. Biol. Chem.* **276**, 7408-7414 (2001).
163 Simonavicius, N. *et al.* Pericytes promote selective vessel regression to regulate vascular patterning. *Blood* **120**, 1516-1527 (2012).
164 Rangel, R. *et al.* Impaired angiogenesis in aminopeptidase N-null mice. *P. Natl. Acad. Sci. USA* **104**, 4588-4593 (2007).
165 Gerlach, J. C. *et al.* Perivascular mesenchymal progenitors in human fetal and adult liver. *Stem cells and development* **21**, 3258-3269 (2012).
166 Chen, J. *et al.* CD146 coordinates brain endothelial cell-pericyte communication for blood-brain barrier development. *Proc. Natl. Acad. Sci.* **114**, 7622-7631 (2017).
167 Aguilera, K. Y. & Brekken, R. A. Recruitment and retention: factors that affect pericyte migration. *Cell Mol. Life Sci.* **71**, 299-309 (2014).
168 Sweeney, M. D., Ayyadurai, S. & Zlokovic, B. V. Pericytes of the neurovascular unit: key functions and signaling pathways. *Nat. Neurosci.* **19**, 771-783 (2016).
169 Reitmeir, R. *et al.* Vascular endothelial growth factor induces contralesional corticobulbar plasticity and functional neurological recovery in the ischemic brain. *Acta Neuropathol.* **123**, 273-284 (2012).
170 Luster, A. D., Unkeless, J. C. & Ravetch, J. V. Gamma-interferon transcriptionally regulates an early-response gene containing homology to platelet proteins. *Nature* **315**, 672-676 (1985).
171 Amin, M. *et al.* Circulatory Levels of C-X-C Motif Chemokine Ligands 1, 9, and 10 Are Elevated in Patients with Ischemic Stroke. *Eurasian J. Med.* **49**, 92-96 (2017).
172 Pekny, M. *et al.* Abnormal reaction to central nervous system injury in mice lacking glial fibrillary acidic protein and vimentin. *J. Cell Biol.* **145**, 503-514 (1999).
173 Flo, T. H. *et al.* Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. *Nature* **432**, 917-921 (2004).
174 Zamanian, J. L. *et al.* Genomic analysis of reactive astrogliosis. *J. Neurosci.* **32**, 6391-6410 (2012).
175 Lian, H. *et al.* NFkappaB-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's disease. *Neuron* **85**, 101-115 (2015).
176 Liddelow, S. A. & Barres, B. A. Reactive Astrocytes: Production, Function, and Therapeutic Potential. *Immunity* **46**, 957-967 (2017).
177 Lin, M. *et al.* Cell surface antigen CD109 is a novel member of the alpha(2) macroglobulin/C3, C4, C5 family of thioester-containing proteins. *Blood* **99**, 1683-1691 (2002).
178 Schuh, A. C. *et al.* A tyrosine703serine polymorphism of CD109 defines the Gov platelet alloantigens. *Blood* **99**, 1692-1698 (2002).
179 Ben-Porath, I. & Benvenisty, N. Characterization of a tumor-associated gene, a member of a novel family of genes encoding membrane glycoproteins. *Gene* **183**, 69-75 (1996).
180 Grenard, P., Bates, M. K. & Aeschlimann, D. Evolution of transglutaminase genes: identification of a transglutaminase gene cluster on human chromosome 15q15. Structure of the gene encoding transglutaminase X and a novel gene family member, transglutaminase Z. *J. Biol. Chem.* **276**, 33066-33078 (2001).
181 Marken, J. S., Schieven, G. L., Hellstrom, I., Hellstrom, K. E. & Aruffo, A. Cloning and expression of the tumor-associated antigen L6. *P. Natl. Acad. Sci. USA* **89**, 3503-3507 (1992).
182 Liddelow, S. A. *et al.* Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* **541**, 481-487 (2017).
183 Stogsdill, J. A. *et al.* Astrocytic neuroligins control astrocyte morphogenesis and synaptogenesis. *Nature* **551**, 192-197 (2017).
184 Ebrahimi, M. *et al.* Astrocyte-expressed FABP 7 regulates dendritic morphology and excitatory synaptic function of cortical neurons. *Glia* **64**, 48-62 (2016).
185 Ma, D. *et al.* Cellular localization of epidermal-type and brain-type fatty acid-binding proteins in adult hippocampus and their response to cerebral ischemia. *Hippocampus* **20**, 811-819 (2010).
186 Hoyaux, D. *et al.* S100A6 overexpression within astrocytes associated with impaired axons from both ALS mouse model and human patients. *J. Neuropath. Exp. Neur.* **61**, 736-744 (2002).

187 Nishiyama, H., Knöpfel, T., Endo, S. & Itohara, S. Glial protein S100B modulates long-term neuronal synaptic plasticity. *Proc. Natl. Acad. Sci.* **99**, 4037-4042 (2002).
188 Wêglewski, A., Ryglewicz, D., Mular, A. & Juryńczyk, J. Changes of protein S100B serum concentration during ischemic and hemorrhagic stroke in relation to the volume of stroke lesion. *Neurol. Neurochir. Pol.* **39**, 310-317 (2005).
189 Nakajima, A. *et al.* Induction of interferon-induced transmembrane protein 3 gene expression by lipopolysaccharide in astrocytes. *Eur. J. Pharmacol.* **745**, 166-175 (2014).
190 Ibi, D. *et al.* Astroglial IFITM3 mediates neuronal impairments following neonatal immune challenge in mice. *Glia* **61**, 679-693 (2013).
191 Lemstra, A. W. *et al.* Microglia activation in sepsis: a case-control study. *J. Neuroinflammation* **4**, 4 (2007).
192 Patel, A. R., Ritzel, R., McCullough, L. D. & Liu, F. Microglia and ischemic stroke: a double-edged sword. *Int. J. Physiol. Pathophysiol. Pharmocol.* **5**, 73-90 (2013).
193 Ito, D., Tanaka, K., Suzuki, S., Dembo, T. & Fukuuchi, Y. Enhanced expression of Iba1, ionized calcium-binding adapter molecule 1, after transient focal cerebral ischemia in rat brain. *Stroke* **32**, 1208-1215 (2001).
194 Pan, J. *et al.* Malibatol A regulates microglia M1/M2 polarization in experimental stroke in a PPARγ-dependent manner. *J. Neuroinflamm.* **12**, 1-11 (2015).
195 Attaai, A. *et al.* Postnatal maturation of microglia is associated with alternative activation and activated TGFβ signaling. *Glia* **66**, 1695-1708 (2018).
196 Herrmann, O. *et al.* IKK mediates ischemia-induced neuronal death. *Nat. Med.* **11**, 1322-1329 (2005).
197 Garlichs, C. *et al.* Upregulation of CD40-CD40 ligand (CD154) in patients with acute cerebral ischemia. *Stroke* **34**, 1412-1418 (2003).
198 Varnum, M. M. & Ikezu, T. The classification of microglial activation phenotypes on neurodegeneration and regeneration in Alzheimer's disease brain. *Arch. Immunol. Ther. Ex.* **60**, 251-266 (2012).
199 Pepe, G., Calderazzi, G., De Maglie, M., Villa, A. M. & Vegeto, E. Heterogeneous induction of microglia M2a phenotype by central administration of interleukin-4. *J. Neuroinflamm.* **11**, 1-14 (2014).
200 Taylor, R. A. & Sansing, L. H. Microglial responses after ischemic stroke and intracerebral hemorrhage. *Clin. Dev. Immunol.* **2013**, 1-10 (2013).
201 Ocaña-Guzman, R., Vázquez-Bolaños, L. & Sada-Ovalle, I. Receptors That Inhibit Macrophage Activation: Mechanisms and Signals of Regulation and Tolerance. *J. Immunol. Res.* **2018**, 1-14 (2018).
202 Griciuc, A. *et al.* Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. *Neuron* **78**, 631-643 (2013).
203 Chakrabarti, A. & Surolia, A. *Biochemical Roles of Eukaryotic Cell Surface Macromolecules* (Springer, 2015).
204 Walker, D. G. & Lue, L.-F. Immune phenotypes of microglia in human neurodegenerative disease: challenges to detecting microglial polarization in human brains. *Alzheimer's Res. Ther.* **7**, 56-64 (2015).
205 Lisi, L. *et al.* Expression of iNOS, CD163 and ARG-1 taken as M1 and M2 markers of microglial polarization in human glioblastoma and the surrounding normal parenchyma. *Neurosci. Lett.* **645**, 106-112 (2017).
206 Sang, M. *et al.* Gene expression profile of peripheral blood mononuclear cells in response to intracerebral hemorrhage. *DNA Cell Biol.* **36**, 647-654 (2017).
207 Cho, S. *et al.* The class B scavenger receptor CD36 mediates free radical production and tissue injury in cerebral ischemia. *J. Neurosci.* **25**, 2504-2512 (2005).
208 Rathore, N. *et al.* Paired Immunoglobulin-like Type 2 Receptor Alpha G78R variant alters ligand binding and confers protection to Alzheimer's disease. *Plos Genet.* **14**, e1007427 (2018).
209 Brown, D., Trowsdale, J. & Allen, R. The LILR family: modulators of innate and adaptive immune pathways in health and disease. *Tissue antigens* **64**, 215-225 (2004).
210 Wei, D., Xiong, X. & Zhao, H. Tim-3 cell signaling and iNOS are involved in the protective effects of ischemic postconditioning against focal ischemia in rats. *Metab. Brain Dis.* **30**, 483-490 (2015).
211 Nagasaki, H. *et al.* Inflammatory changes in adipose tissue enhance expression of GPR84, a medium-chain fatty acid receptor: TNFα enhances GPR84 expression in adipocytes. *FEBS Lett.* **586**, 368-372 (2012).
212 Fernandez-Cadenas, I. *et al.* Genes involved in hemorrhagic transformations that follow recombinant t-PA treatment in stroke patients. *Pharmacogenomics* **14**, 495-504 (2013).
213 Shichita, T. *et al.* MAFB prevents excess inflammation after ischemic stroke by accelerating clearance of damage signals through MSR1. *Nat. Med.* **23**, 723-732 (2017).
214 Kraal, G., van der Laan, L. J., Elomaa, O. & Tryggvason, K. The macrophage receptor MARCO. *Microbes Infect.* **2**, 313-316 (2000).
215 Lozano, E., Joller, N., Cao, Y., Kuchroo, V. K. & Hafler, D. A. The CD226/CD155 interaction regulates the proinflammatory (Th1/Th17)/anti-inflammatory (Th2) balance in humans. *J. Immunol.* **191**, 3673-3680 (2013).
216 Zhou, M., Wang, C. M., Yang, W.-L. & Wang, P. Microglial CD14 activated by iNOS contributes to neuroinflammation in cerebral ischemia. *Brain Res.* **1506**, 105-114 (2013).
217 Deng, Q.-W. *et al.* Blocking sympathetic nervous system reverses partially stroke-induced immunosuppression but does not aggravate functional outcome after experimental stroke in rats. *Neurochem. Res.* **41**, 1877-1886 (2016).
218 Garcia-Guzman, M., Soto, F., Gomez-Hernandez, J. M., Lund, P. E. & Stuhmer, W. Characterization of recombinant human P2X4 receptor reveals pharmacological differences to the rat homologue. *Mol. Pharmacol.* **51**, 109-118 (1997).
219 Burnstock, G. Discovery of purinergic signalling, the initial resistance and current explosion of interest. *Br. J. Pharmacol.* **167**, 238-255 (2012).

220 Cavaliere, F. *et al.* Up-regulation of P2X2, P2X4 receptor and ischemic cell death: prevention by P2 antagonists. *Neuroscience* **120**, 85-98 (2003).
221 Somers, G. R. *et al.* Chromosomal localization of the human P2y6 purinoceptor gene and phylogenetic analysis of the P2y purinoceptor family. *Genomics* **44**, 127-130 (1997).
222 Yuan, L. Y., He, Z. Y., Li, L. & Wang, Y. Z. Association of G-protein coupled purinergic receptor P2Y2 with ischemic stroke in a Han Chinese population of North China. *Neural Regen Res.* **14**, 506-512 (2019).
223 Rassendren, F. *et al.* The permeabilizing ATP receptor, P2X7. Cloning and expression of a human cDNA. *J. Biol. Chem.* **272**, 5482-5486 (1997).
224 Domercq, M. *et al.* P2X7 receptors mediate ischemic damage to oligodendrocytes. *Glia* **58**, 730-740 (2010).
225 Hollopeter, G. *et al.* Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature* **409**, 202-207 (2001).
226 Lou, N. *et al.* Purinergic receptor P2RY12-dependent microglial closure of the injured blood-brain barrier. *P. Natl. Acad. Sci. USA* **113**, 1074-1079 (2016).
227 Ayyanathan, K. *et al.* Cloning and chromosomal localization of the human P2Y1 purinoceptor. *Biochem. Bioph. Res. Co.* **218**, 783-788 (1996).
228 Kuboyama, K. *et al.* Astrocytic P2Y(1) receptor is involved in the regulation of cytokine/chemokine transcription and cerebral damage in a rat model of cerebral ischemia. *J. Cerebr. Blood F.* **31**, 1930-1941 (2011).
229 Bruno, V. M. *et al.* Salmonella Typhimurium type III secretion effectors stimulate innate immune responses in cultured epithelial cells. *Plos Pathog.* **5**, e1000538 (2009).
230 Kamme, F., Campbell, K. & Wieloch, T. Biphasic expression of the fos and jun families of transcription factors following transient forebrain ischaemia in the rat. Effect of hypothermia. *Eur. J. Neurosci.* **7**, 2007-2016 (1995).
231 Hao, N. & Whitelaw, M. L. The emerging roles of AhR in physiology and immunity. *Biochem. Pharmacol.* **86**, 561-570 (2013).
232 Cuartero, M. I. *et al.* L-kynurenine/aryl hydrocarbon receptor pathway mediates brain damage after experimental stroke. *Circulation* **130**, 2040-2051 (2014).
233 Cao, Z. *et al.* Kruppel-like factor KLF10 targets transforming growth factor-β1 to regulate CD4+ CD25− T cells and T regulatory cells. *J. Biol. Chem.* **284**, 24914-24924 (2009).
234 Zamanian, J. L. *et al.* Genomic analysis of reactive astrogliosis. *J. Neurosci.* **32**, 6391-6410 (2012).
235 Savitsky, D., Tamura, T., Yanai, H. & Taniguchi, T. Regulation of immunity and oncogenesis by the IRF transcription factor family. *Cancer Immunol. Immun.* **59**, 489-510 (2010).
236 Xiang, M. *et al.* Interferon regulatory factor 8 protects against cerebral ischaemic-reperfusion injury. *J. Neurochem.* **129**, 988-1001 (2014).
237 Perini, F. *et al.* Temporal profile of serum anti-inflammatory and pro-inflammatory interleukins in acute ischemic stroke patients. *Neurol. Sci.* **22**, 289-296 (2001).
238 Osei, Y. D. & Churchich, J. E. Screening and sequence determination of a cDNA encoding the human brain 4-aminobutyrate aminotransferase. *Gene* **155**, 185-187 (1995).
239 Dong, H. *et al.* Excessive expression of acetylcholinesterase impairs glutamatergic synaptogenesis in hippocampal neurons. *J. Neurosci.* **24**, 8950-8960 (2004).
240 Cunha, R. A. Neuroprotection by adenosine in the brain: from A 1 receptor activation to A 2A receptor blockade. *Purinerg. Signal.* **1**, 111-134 (2005).
241 FERRÉ, S. *et al.* Role of adenosine in the control of homosynaptic plasticity in striatal excitatory synapses. *J. Integr. Neurosci.* **4**, 445-464 (2005).
242 Lee, H. T., Gallos, G., Nasr, S. H. & Emala, C. W. A1 adenosine receptor activation inhibits inflammation, necrosis, and apoptosis after renal ischemia-reperfusion injury in mice. *J. Am. Soc. Nephrol.* **15**, 102-111 (2004).
243 Benito-Muñoz, M., Matute, C. & Cavaliere, F. Adenosine A1 receptor inhibits postnatal neurogenesis and sustains astrogliogenesis from the subventricular zone. *Glia* **64**, 1465-1478 (2016).
244 Haas, H. L. & Selbach, O. Functions of neuronal adenosine receptors. *N-S Arch. Pharmacol.* **362**, 375-381 (2000).
245 Zhan, Q. & Tang, M. Research advances on apoptosis caused by quantum dots. *Biol. Trace Elem. Res.* **161**, 3-12 (2014).
246 Horgusluoglu-Moloch, E. *et al.* Targeted neurogenesis pathway-based gene analysis identifies ADORA2A associated with hippocampal volume in mild cognitive impairment and Alzheimer's disease. *Neurobiol. Aging* **60**, 92-103 (2017).
247 Ohta, A. & Sitkovsky, M. Role of G-protein-coupled adenosine receptors in downregulation of inflammation and protection from tissue damage. *Nature* **414**, 916-920 (2001).
248 Marcato, P., Dean, C. A., Giacomantonio, C. A. & Lee, P. W. Aldehyde dehydrogenase: its role as a cancer stem cell marker comes down to the specific isoform. *Cell Cycle* **10**, 1378-1384 (2011).
249 Zamo, A. *et al.* Anaplastic lymphoma kinase (ALK) activates Stat3 and protects hematopoietic cells from cell death. *Oncogene* **21**, 1038 (2002).
250 Cazes, A. *et al.* Activated Alk triggers prolonged neurogenesis and Ret upregulation providing a therapeutic target in ALK-mutated neuroblastoma. *Oncotarget* **5**, 2688 (2014).
251 Li, W., Chan, W. W. R., Ngo, J. C. K. & Lau, K.-F. Emerging roles of the neural adaptor FE65 in neurite outgrowth. *Neural Regen. Res.* **13**, 2085-2086 (2018).

252 Forni, P. E., Fornaro, M., Guénette, S. & Wray, S. A role for FE65 in controlling GnRH-1 neurogenesis. *J. Neurosci.* **31**, 480-491 (2011).
253 Bruni, P. *et al.* Fe65, a ligand of the Alzheimer's β-amyloid precursor protein, blocks cell cycle progression by down-regulating thymidylate synthase expression. *J. Biol. Chem.* **277**, 35481-35488 (2002).
254 Korwek, K. M., Trotter, J. H., LaDu, M. J., Sullivan, P. M. & Weeber, E. J. ApoE isoform-dependent changes in hippocampal synaptic function. *Mol. Neurodegener.* **4**, 21 (2009).
255 Poirier, J., Minnich, A. & Davignon, J. Apolipoprotein E, synaptic plasticity and Alzheimer's disease. *Ann. Med.* **27**, 663-670 (1995).
256 Elliott, D. A., Kim, W. S., Jans, D. A. & Garner, B. Apoptosis induces neuronal apolipoprotein-E synthesis and localization in apoptotic bodies. *Neurosci. Lett.* **416**, 206-210 (2007).
257 Schinder, A. F. & Morgenstern, N. A. Adult neurogenesis is altered by GABAergic imbalance in models of Alzheimer's disease. *Cell Stem Cell* **5**, 573-574 (2009).
258 Ikin, A. F., Sabo, S. L., Lanier, L. M. & Buxbaum, J. D. A macromolecular complex involving the amyloid precursor protein (APP) and the cytosolic adapter FE65 is a negative regulator of axon branching. *Mol. Cell. Neurosci.* **35**, 57-63 (2007).
259 Zhou, Z.-d. *et al.* The roles of amyloid precursor protein (APP) in neurogenesis: Implications to pathogenesis and therapy of Alzheimer disease. *Cell Adhes. Migr.* **5**, 280-292 (2011).
260 Andres, R. *et al.* Multiple effects of artemin on sympathetic neurone generation, survival and growth. *Development* **128**, 3685-3695 (2001).
261 Pacary, E. *et al.* Proneural transcription factors regulate different steps of cortical neuron migration through Rnd-mediated inhibition of RhoA signaling. *Neuron* **69**, 1069-1084 (2011).
262 Hardwick, L. J. & Philpott, A. Nervous decision-making: to divide or differentiate. *Trends Genet.* **30**, 254-261 (2014).
263 Hockenbery, D., Nuñez, G., Milliman, C., Schreiber, R. D. & Korsmeyer, S. J. Bcl-2 is an inner mitochondrial membrane protein that blocks programmed cell death. *Nature* **348**, 334-336 (1990).
264 Zhang, R. *et al.* Bcl-2 enhances neurogenesis and inhibits apoptosis of newborn neurons in adult rat brain following a transient middle cerebral artery occlusion. *Neurobiol. Dis.* **24**, 345-356 (2006).
265 Shetty, A. K. & Turner, D. A. In vitro survival and differentiation of neurons derived from epidermal growth factor-responsive postnatal hippocampal stem cells: inducing effects of brain-derived neurotrophic factor. *J. Neurobiol.* **35**, 395-425 (1998).
266 Bramham, C. R. & Messaoudi, E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Prog. Neurobiol.* **76**, 99-125 (2005).
267 Lim, D. A. *et al.* Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. *Neuron* **28**, 713-726 (2000).
268 Shetty, G. A., Hattiangady, B. & Shetty, A. K. Neural stem cell-and neurogenesis-related gene expression profiles in the young and aged dentate gyrus. *Age* **35**, 2165-2176 (2013).
269 Moncini, S. *et al.* The role of miR-103 and miR-107 in regulation of CDK5R1 expression and in cellular migration. *Plos One* **6**, e20038 (2011).
270 Buchman, J. J. *et al.* Cdk5rap2 interacts with pericentrin to maintain the neural progenitor pool in the developing neocortex. *Neuron* **66**, 386-402 (2010).
271 Pattyn, A., Morin, X., Cremer, H., Goridis, C. & Brunet, J.-F. Expression and interactions of the two closely related homeobox genes Phox2a and Phox2b during neurogenesis. *Development* **124**, 4065-4075 (1997).
272 Gosso, M. *et al.* Association between the CHRM2 gene and intelligence in a sample of 304 Dutch families. *Genes Brain Behav.* **5**, 577-584 (2006).
273 Dworkin, S. & Mantamadiotis, T. Targeting CREB signalling in neurogenesis. *Expert Opin. Ther. Tar.* **14**, 869-879 (2010).
274 Carlezon Jr, W. A., Duman, R. S. & Nestler, E. J. The many faces of CREB. *Trends Neurosci.* **28**, 436-445 (2005).
275 Edman, L. C. *et al.* α-Chemokines Regulate Proliferation, Neurogenesis, and Dopaminergic Differentiation of Ventral Midbrain Precursors and Neurospheres. *Stem Cells* **26**, 1891-1900 (2008).
276 Furusato, B., Mohamed, A., Uhlén, M. & Rhim, J. S. CXCR4 and cancer. *Pathol. Int.* **60**, 497-505 (2010).
277 Manent, J.-B., Wang, Y., Chang, Y., Paramasivam, M. & LoTurco, J. J. Dcx reexpression reduces subcortical band heterotopia and seizure threshold in an animal model of neuronal migration disorder. *Nat. Med.* **15**, 84-90 (2008).
278 Deuel, T. A. *et al.* Genetic interactions between doublecortin and doublecortin-like kinase in neuronal migration and axon outgrowth. *Neuron* **49**, 41-53 (2006).
279 Artavanis-Tsakonas, S., Matsuno, K. & Fortini, M. E. Notch signaling. *Science* **268**, 225-232 (1995).
280 Mizuhara, E. *et al.* MAGI1 recruits Dll1 to cadherin-based adherens junctions and stabilizes it on the cell surface. *J. Biol. Chem.* **280**, 26499-26507 (2005).
281 Ramos, C., Rocha, S., Gaspar, C. & Henrique, D. Two Notch ligands, Dll1 and Jag1, are differently restricted in their range of action to control neurogenesis in the mammalian spinal cord. *Plos One* **5**, e15515 (2010).
282 Shimojo, H. & Kageyama, R. in *Semin. Cell Dev. Biol.* 76-82 (Elsevier).
283 Pecina, M. *et al.* DRD2 polymorphisms modulate reward and emotion processing, dopamine neurotransmission and openness to experience. *Cortex* **49**, 877-890 (2013).
284 Cazorla, M. *et al.* Dopamine D2 receptors regulate the anatomical and functional balance of basal ganglia circuitry. *Neuron* **81**, 153-164 (2014).

285 Crandall, J. E. *et al.* Dopamine receptor activation modulates GABA neuron migration from the basal forebrain to the cerebral cortex. *J. Neurosci.* **27**, 3813-3822 (2007).
286 Sillivan, S. E. *Dopamine Receptor Stimulation Regulates Expression of Developmental Genes and Disrupts Netrin-1-Mediated Axon Guidance*, Vanderbilt University, (2011).
287 Shen, W., Flajolet, M., Greengard, P. & Surmeier, D. J. Dichotomous dopaminergic control of striatal synaptic plasticity. *Science* **321**, 848-851 (2008).
288 Kern, A., Albarran-Zeckler, R., Walsh, H. E. & Smith, R. G. Apo-ghrelin receptor forms heteromers with DRD2 in hypothalamic neurons and is essential for anorexigenic effects of DRD2 agonism. *Neuron* **73**, 317-332 (2012).
289 Zhang, L., Yang, X., Yang, S. & Zhang, J. The Wnt/β-catenin signaling pathway in the adult neurogenesis. *Eur. J. Neurosci.* **33**, 1-8 (2011).
290 Ahmad-Annuar, A. *et al.* Signaling across the synapse: a role for Wnt and Dishevelled in presynaptic assembly and neurotransmitter release. *J. Cell Biol.* **174**, 127-139 (2006).
291 Varela-Nallar, L. & Inestrosa, N. C. Wnt signaling in the regulation of adult hippocampal neurogenesis. *Front Cell Neurosci.* **7**, 100 (2013).
292 Arvanitis, D. N. *et al.* Ephrin B1 maintains apical adhesion of neural progenitors. *Development*, 2082-2092 (2013).
293 Riese, D. J. & Stern, D. F. Specificity within the EGF family/ErbB receptor family signaling network. *Bioessays* **20**, 41-48 (1998).
294 Jin, K. *et al.* Heparin-binding epidermal growth factor-like growth factor: hypoxia-inducible expression in vitro and stimulation of neurogenesis in vitro and in vivo. *J. Neurosci.* **22**, 5365-5373 (2002).
295 Attar, N. & Kurdistani, S. K. Exploitation of EP300 and CREBBP lysine acetyltransferases by cancer. *CSH Perspect. Med.*, a026534 (2016).
296 Asaduzzaman, M. *et al.* Tumour suppressor EP300, a modulator of paclitaxel resistance and stemness, is downregulated in metaplastic breast cancer. *Breast Cancer Res. Tr.* **163**, 461-474 (2017).
297 Petro, K. A. & Schengrund, C.-L. Membrane raft disruption promotes axonogenesis in n2a neuroblastoma cells. *Neurochem. Res.* **34**, 29-37 (2009).
298 Fukata, Y. & Fukata, M. Protein palmitoylation in neuronal development and synaptic plasticity. *Nat. Rev. Neurosci.* **11**, 161-175 (2010).
299 Polo-Parada, L., Bose, C. M. & Landmesser, L. T. Alterations in transmission, vesicle dynamics, and transmitter release machinery at NCAM-deficient neuromuscular junctions. *Neuron* **32**, 815-828 (2001).
300 Raballo, R. *et al.* Basic fibroblast growth factor (Fgf2) is necessary for cell proliferation and neurogenesis in the developing cerebral cortex. *J. Neurosci.* **20**, 5012-5023 (2000).
301 Walicke, P. Basic and acidic fibroblast growth factors have trophic effects on neurons from multiple CNS regions. *J. Neurosci.* **8**, 2618-2627 (1988).
302 Zhang, L. *et al.* MEK-ERK1/2-dependent FLNA overexpression promotes abnormal dendritic patterning in tuberous sclerosis independent of mTOR. *Neuron* **84**, 78-91 (2014).
303 Houlihan, S. L., Lanctot, A. A., Guo, Y. & Feng, Y. Upregulation of neurovascular communication through filamin abrogation promotes ectopic periventricular neurogenesis. *Elife* **5**, e17823 (2016).
304 Manabe, Y. *et al.* Adenovirus-mediated gene transfer of glial cell line-derived neurotrophic factor prevents motor neuron loss of transgenic model mice for amyotrophic lateral sclerosis. *Apoptosis* **7**, 329-334 (2002).
305 Chen, Y., Ai, Y., Slevin, J. R., Maley, B. E. & Gash, D. M. Progenitor proliferation in the adult hippocampus and substantia nigra induced by glial cell line-derived neurotrophic factor. *Exp. Neurol.* **196**, 87-95 (2005).
306 Lin, L. F., Doherty, D. H., Lile, J. D., Bektesh, S. & Collins, F. GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science* **260**, 1130-1132 (1993).
307 Cull-Candy, S., Brickley, S. & Farrant, M. NMDA receptor subunits: diversity, development and disease. *Curr. Opin. Neurobio.* **11**, 327-335 (2001).
308 Hasan, M. T. *et al.* Role of motor cortex NMDA receptors in learning-dependent synaptic plasticity of behaving mice. *Nat. Commun.* **4** (2013).
309 Majdzadeh, N. *et al.* HDAC4 inhibits cell-cycle progression and protects neurons from cell death. *De. Neurobiol.* **68**, 1076-1092 (2008).
310 Zhang, J. *et al.* microRNA-22, downregulated in hepatocellular carcinoma and correlated with prognosis, suppresses cell proliferation and tumourigenicity. *Brit. J. Cancer* **103**, 1215 (2010).
311 Liu, J. *et al.* Role of phosphorylated HDAC4 in stroke-induced angiogenesis. *Biomed Res. Int.* **2017** (2017).
312 Bae, S., Bessho, Y., Hojo, M. & Kageyama, R. The bHLH gene Hes6, an inhibitor of Hes1, promotes neuronal differentiation. *Development* **127**, 2933-2943 (2000).
313 Xiao, M.-J., Han, Z., Shao, B. & Jin, K. Notch signaling and neurogenesis in normal and stroke brain. *Int. J. Physiol. Pathophysiol. Pharmocol.* **1**, 192 (2009).
314 Sakamoto, M., Hirata, H., Ohtsuka, T., Bessho, Y. & Kageyama, R. The basic helix-loop-helix genes Hesr1/Hey1 and Hesr2/Hey2 regulate maintenance of neural precursor cells in the brain. *J. Biol. Chem.* **278**, 44808-44815 (2003).
315 Jalali, A. *et al.* HeyL promotes neuronal differentiation of neural progenitor cells. *J. Neurosci. Res.* **89**, 299-309 (2011).
316 Bergui, L., Schena, M., Gaidano, G., Riva, M. & Caligaris-Cappio, F. Interleukin 3 and interleukin 6 synergistically promote the proliferation and differentiation of malignant plasma cell precursors in multiple myeloma. *J. Exp. Med.* **170**, 613-618 (1989).

317 Kannan, Y. *et al.* Neurotrophic action of interleukin 3 and granulocyte-macrophage colony-stimulating factor on murine sympathetic neurons. *Neuroimmunomodulation* **8**, 132-141 (2000).
318 Farrell, K., Mahajan, G., Srinivasan, P., Lee, M.-Y. & Kothapalli, C. R. Pediatric glioblastoma cells inhibit neurogenesis and promote astrogenesis, phenotypic transformation and migration of human neural progenitor cells within cocultures. *Exp. Cell Res.* **362**, 159-171 (2018).
319 Huang, Y. C. *et al.* The epigenetic factor Kmt2a/Mll1 regulates neural progenitor proliferation and neuronal and glial differentiation. *De. Neurobiol.* **75**, 452-462 (2015).
320 Oshima, K., Teo, D. T. W., Senn, P., Starlinger, V. & Heller, S. LIF promotes neurogenesis and maintains neural precursors in cell populations derived from spiral ganglion stem cells. *BMC Dev. Biol.* **7**, 112 (2007).
321 Curtis, R. *et al.* Retrograde axonal transport of LIF is increased by peripheral nerve injury: correlation with increased LIF expression in distal nerve. *Neuron* **12**, 191-204 (1994).
322 Dehmelt, L. & Halpain, S. The MAP2/Tau family of microtubule-associated proteins. *Genome Biol.* **6**, 204 (2005).
323 Luo, J. *et al.* Midkine-A functions upstream of Id2a to regulate cell cycle kinetics in the developing vertebrate retina. *Neural Dev.* **7**, 1-15 (2012).
324 Kikuchi-Horie, K. *et al.* Distinctive expression of midkine in the repair period of rat brain during neurogenesis: immunohistochemical and immunoelectron microscopic observations. *J. Neurosci. Res.* **75**, 678-687 (2004).
325 Winkler, C. & Yao, S. The midkine family of growth factors: diverse roles in nervous system formation and maintenance. *Brit. J. Pharmacol.* **171**, 905-912 (2014).
326 Rawnaq, T. *et al.* The multifunctional growth factor midkine promotes proliferation and migration in pancreatic cancer. *Mol. Cancer Res.* (2014).
327 Li, H. *et al.* Transcription factor MEF2C influences neural stem/progenitor cell differentiation and maturation in vivo. *Proc. Natl. Acad. Sci.* **105**, 9397-9402 (2008).
328 Skerjanc, I. S. & Wilton, S. Myocyte enhancer factor 2C upregulates MASH-1 expression and induces neurogenesis in P19 cells. *FEBS Lett.* **472**, 53-56 (2000).
329 Gao, Z. *et al.* Neurod1 is essential for the survival and maturation of adult-born neurons. *Nat. Neurosci.* **12**, 1090-1092 (2009).
330 Dixit, R. *et al.* Neurog1 and Neurog2 control two waves of neuronal differentiation in the piriform cortex. *J. Neurosci.* **34**, 539-553 (2014).
331 Heng, J. I.-T. *et al.* Neurogenin 2 controls cortical neuron migration through regulation of Rnd2. *Nature* **455**, 114-118 (2008).
332 Park, C. S., Zhong, L. & Tang, S. J. Aberrant expression of synaptic plasticity-related genes in the NF1+/− mouse hippocampus. *J. Neurosci. Res.* **87**, 3107-3119 (2009).
333 Berezovska, O. *et al.* Notch1 inhibits neurite outgrowth in postmitotic primary neurons. *Neuroscience* **93**, 433-439 (1999).
334 Engler, A. *et al.* Notch2 signaling maintains NSC quiescence in the murine ventricular-subventricular zone. *Cell Rep.* **22**, 992-1002 (2018).
335 Muramatsu, T. Midkine and pleiotrophin: two related proteins involved in development, survival, inflammation and tumorigenesis. *J. Biochem.* **132**, 359-371 (2002).
336 Lindsell, C. E., Boulter, J., Gossler, A. & Weinmaster, G. Expression Patterns ofJagged, Delta1, Notch1, Notch2, andNotch3Genes Identify Ligand–Receptor Pairs That May Function in Neural Development. *Mol. Cell. Neurosci.* **8**, 14-27 (1996).
337 Davis, J. Q. & Bennett, V. Ankyrin binding activity shared by the neurofascin/L1/NrCAM family of nervous system cell adhesion molecules. *J. Biol. Chem.* **269**, 27163-27166 (1994).
338 Sakurai, T. The role of NrCAM in neural development and disorders—beyond a simple glue in the brain. *Mol. Cell. Neurosci.* **49**, 351-363 (2012).
339 Zelina, P., Avci, H. X., Thelen, K. & Pollerberg, G. E. The cell adhesion molecule NrCAM is crucial for growth cone behaviour and pathfinding of retinal ganglion cell axons. *Development* **132**, 3609-3618 (2005).
340 Morrison, S. J. *et al.* Transient Notch activation initiates an irreversible switch from neurogenesis to gliogenesis by neural crest stem cells. *Cell* **101**, 499-510 (2000).
341 Liu, Y., Ford, B. D., Mann, M. A. & Fischbach, G. D. Neuregulin-1 increases the proliferation of neuronal progenitors from embryonic neural stem cells. *Dev. Biol.* **283**, 437-445 (2005).
342 Scharfman, H. *et al.* Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. *Exp. Neurol.* **192**, 348-356 (2005).
343 Fujisawa, H. *et al.* Roles of a neuronal cell-surface molecule, neuropilin, in nerve fiber fasciculation and guidance. *Cell Tissue Res.* **290**, 465-470 (1997).
344 Parthasarathy, S., Srivatsa, S., Nityanandam, A. & Tarabykin, V. Ntf3 acts downstream of Sip1 in cortical postmitotic neurons to control progenitor cell fate through feedback signaling. *Development* **141**, 3324-3330 (2014).
345 Zhou, Q. & Anderson, D. J. The bHLH transcription factors OLIG2 and OLIG1 couple neuronal and glial subtype specification. *Cell* **109**, 61-73 (2002).
346 Garcia-Guzman, M., Soto, F., Gomez-Hernandez, J. M., Lund, P.-E. & Stühmer, W. Characterization of recombinant human P2X4 receptor reveals pharmacological differences to the rat homologue. *Mol. Pharmacol.* **51**, 109-118 (1997).
347 Burnstock, G. Discovery of purinergic signalling, the initial resistance and current explosion of interest. *Brit. J. Pharmacol.* **167**, 238-255 (2012).

348 Cavaliere, F. *et al.* Up-regulation of P2X2, P2X4 receptor and ischemic cell death: prevention by P2 antagonists. *Neuroscience* **120**, 85-98 (2003).
349 Ayyanathan, K. *et al.* Cloning and chromosomal localization of the human P2Y1 purinoceptor. *Biochem. Bioph. Res. Commun.* **218**, 783-788 (1996).
350 Kuboyama, K. *et al.* Astrocytic P2Y1 receptor is involved in the regulation of cytokine/chemokine transcription and cerebral damage in a rat model of cerebral ischemia. *J. Cerebr. Blood F. Met.* **31**, 1930-1941 (2011).
351 Somers, G. R. *et al.* Chromosomal Localization of the Human P2y6Purinoceptor Gene and Phylogenetic Analysis of the P2y Purinoceptor Family. *Genomics* **44**, 127-130 (1997).
352 Yuan, L.-Y., He, Z.-Y., Li, L. & Wang, Y.-Z. Association of G-protein coupled purinergic receptor P2Y2 with ischemic stroke in a Han Chinese population of North China. *Neural Regen. Res.* **14**, 506-512 (2019).
353 Hirotsune, S. *et al.* Graded reduction of Pafah1b1 (Lis1) activity results in neuronal migration defects and early embryonic lethality. *Nat. Genet.* **19**, 333-339 (1998).
354 Matus, A. Microtubule-associated proteins: their potential role in determining neuronal morphology. *Annu. Rev. Neurosci.* **11**, 29-44 (1988).
355 Dinday, M. T., Girskis, K. M., Lee, S., Baraban, S. C. & Hunt, R. F. PAFAH1B1 haploinsufficiency disrupts GABA neurons and synaptic E/I balance in the dentate gyrus. *Sci. Rep.* **7**, 8269 (2017).
356 Wang, Y.-Y. *et al.* In vitro growth conditions and development affect differential distributions of RNA in axonal growth cones and shafts of cultured rat hippocampal neurons. *Mol. Cell. Neurosci.* **61**, 141-151 (2014).
357 Zhong, W. & Chia, W. Neurogenesis and asymmetric cell division. *Curr. Opin. Neurobio.* **18**, 4-11 (2008).
358 Tan, X. & Shi, S. H. Neocortical neurogenesis and neuronal migration. *Wiley Interdiscip. Rev. Dev. Biol.* **2**, 443-459 (2013).
359 Castelo-Branco, G. *et al.* Ventral midbrain glia express region-specific transcription factors and regulate dopaminergic neurogenesis through Wnt-5a secretion. *Mol. Cell. Neurosci.* **31**, 251-262 (2006).
360 Dude, C. M. *et al.* Activation of Pax3 target genes is necessary but not sufficient for neurogenesis in the ophthalmic trigeminal placode. *Dev. Biol.* **326**, 314-326 (2009).
361 Moley, K. H. Hyperglycemia and apoptosis: mechanisms for congenital malformations and pregnancy loss in diabetic women. *Trends Endocrin. Met.* **12**, 78-82 (2001).
362 Osumi, N., Shinohara, H., Numayama-Tsuruta, K. & Maekawa, M. Concise review: Pax6 transcription factor contributes to both embryonic and adult neurogenesis as a multifunctional regulator. *Stem Cells* **26**, 1663-1672 (2008).
363 Dominguez, M. H., Ayoub, A. E. & Rakic, P. POU-III transcription factors (Brn1, Brn2, and Oct6) influence neurogenesis, molecular identity, and migratory destination of upper-layer cells of the cerebral cortex. *Cereb. Cortex* **23**, 2632-2643 (2012).
364 Wu, Y. & Wu, P. Y. CD133 as a marker for cancer stem cells: progresses and concerns. *Stem Cells Dev.* **18**, 1127-1134 (2009).
365 Weng, T. *et al.* Pleiotrophin regulates lung epithelial cell proliferation and differentiation during fetal lung development via β-catenin and Dlk1. *J. Biol. Chem.*, jbc. M109. 052530 (2009).
366 Mentlein, R. & Held-Feindt, J. Pleiotrophin, an angiogenic and mitogenic growth factor, is expressed in human gliomas. *J. Neurochem.* **83**, 747-753 (2002).
367 Kadomatsu, K. & Muramatsu, T. Midkine and pleiotrophin in neural development and cancer. *Cancer Lett.* **204**, 127-143 (2004).
368 Hajdo-Milašinović, A., Ellenbroek, S. I., van Es, S., van der Vaart, B. & Collard, J. G. Rac1 and Rac3 have opposing functions in cell adhesion and differentiation of neuronal cells. *J. Cell Sci.* **120**, 555-566 (2007).
369 Andrews, W. *et al.* Robo1 regulates the development of major axon tracts and interneuron migration in the forebrain. *Development* **133**, 2243-2252 (2006).
370 Rhee, J., Buchan, T., Zukerberg, L., Lilien, J. & Balsamo, J. Cables links Robo-bound Abl kinase to N-cadherin-bound β-catenin to mediate Slit-induced modulation of adhesion and transcription. *Nat. Cell Biol.* **9**, 883-892 (2007).
371 GrandPré, T., Nakamura, F., Vartanian, T. & Strittmatter, S. M. Identification of the Nogo inhibitor of axon regeneration as a Reticulon protein. *Nature* **403**, 439-444 (2000).
372 Philippidou, P., Walsh, C. M., Aubin, J., Jeannotte, L. & Dasen, J. S. Sustained Hox5 gene activity is required for respiratory motor neuron development. *Nat. Neurosci.* **15**, 1636-1644 (2012).
373 Schäfer, B. W. & Heizmann, C. W. The S100 family of EF-hand calcium-binding proteins: functions and pathology. *Trends Biochem. Sci.* **21**, 134-140 (1996).
374 Reeves, R. H. *et al.* Astrocytosis and axonal proliferation in the hippocampus of S100b transgenic mice. *Proc. Natl. Acad. Sci.* **91**, 5359-5363 (1994).
375 Mu, Y., Lee, S. W. & Gage, F. H. Signaling in adult neurogenesis. *Curr. Opin. Neurobio.* **20**, 416-423 (2010).
376 Joksimovic, M. *et al.* Wnt antagonism of Shh facilitates midbrain floor plate neurogenesis. *Nat. Neurosci.* **12**, 125-131 (2009).
377 Hu, H. Chemorepulsion of neuronal migration by Slit2 in the developing mammalian forebrain. *Neuron* **23**, 703-711 (1999).
378 Hu, H. Cell-surface heparan sulfate is involved in the repulsive guidance activities of Slit2 protein. *Nat. Neurosci.* **4**, 695-701 (2001).
379 Magrané, J., Sahawneh, M. A., Przedborski, S., Estévez, Á. G. & Manfredi, G. Mitochondrial dynamics and bioenergetic dysfunction is associated with synaptic alterations in mutant SOD1 motor neurons. *J. Neurosci.* **32**, 229-242 (2012).

380 Sarkar, A. & Hochedlinger, K. The sox family of transcription factors: versatile regulators of stem and progenitor cell fate. *Cell Stem Cell* **12**, 15-30 (2013).
381 Stolt, C. C., Lommes, P., Friedrich, R. P. & Wegner, M. Transcription factors Sox8 and Sox10 perform non-equivalent roles during oligodendrocyte development despite functional redundancy. *Development* **131**, 2349-2358 (2004).
382 van Velthoven, C. T., Kavelaars, A., van Bel, F. & Heijnen, C. J. Mesenchymal stem cell transplantation changes the gene expression profile of the neonatal ischemic brain. *Brain Behav. Immun.* **25**, 1342-1348 (2011).
383 Gu, F. *et al.* Suppression of Stat3 promotes neurogenesis in cultured neural stem cells. *J. Neurosci. Res.* **81**, 163-171 (2005).
384 Brionne, T. C., Tesseur, I., Masliah, E. & Wyss-Coray, T. Loss of TGF-β1 leads to increased neuronal cell death and microgliosis in mouse brain. *Neuron* **40**, 1133-1145 (2003).
385 He, Y. *et al.* ALK5-dependent TGF-β signaling is a major determinant of late-stage adult neurogenesis. *Nat. Neurosci.* **17**, 943-952 (2014).
386 Winner, B. *et al.* Striatal deafferentation increases dopaminergic neurogenesis in the adult olfactory bulb. *Exp. Neurol.* **197**, 113-121 (2006).
387 Das, S. & Basu, A. Inflammation: a new candidate in modulating adult neurogenesis. *J. Neurosci. Res.* **86**, 1199-1208 (2008).
388 Pesheva, P., Gloor, S., Schachner, M. & Probstmeier, R. Tenascin-R is an intrinsic autocrine factor for oligodendrocyte differentiation and promotes cell adhesion by a sulfatidemediated mechanism. *J. Neurosci.* **17**, 4642-4651 (1997).