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REVIEW ARTICLE

Netrin-1 in Post-stroke Neuroprotection: Beyond Axon Guidance Cue

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Abstract: ***Background*:** Stroke, especially ischemic stroke, is a leading disease associated with death and long-term disability with limited therapeutic options. Neuronal death caused by vascular impairment, programmed cell death and neuroinflammation has been proven to be associated with increased stroke severity and poor stroke recovery. In light of this, a development of neuroprotective drugs targeting injured neurons is urgently needed for stroke treatment. Netrin-1, known as a bifunctional molecule, was originally described to mediate the repulsion or attraction of axonal growth by interacting with its different receptors. Importantly, accumulating evidence has shown that netrin-1 can manifest its beneficial functions to brain tissue repair and neural regeneration in different neurological disease models.

***Objective*:** In this review, we focus on the implications of netrin-1 and its possibly involved pathways on neuroprotection after ischemic stroke, through which a better understanding of the underlying mechanisms of netrin-1 may pave the way to novel treatments.

***Methods*:** Peer-reviewed literature was recruited by searching databases of PubMed, Scopus, Embase, and Web of Science till the year 2021.

***Conclusion*:** There has been certain evidence to support the neuroprotective function of netrin-1 by regulating angiogenesis, autophagy, apoptosis and neuroinflammation after stroke. Netrin-1 may be a promising drug candidate in reducing stroke severity and improving outcomes.

Keywords: Netrin-1, angiogenesis, apoptosis, autophagy, neuroinflammation, neuroprotection, cerebral ischemia.

1. INTRODUCTION

Stroke, a leading cause of death and long-term disability, has been one of the increasing global burdens of disease worldwide [1]. About 87% of all strokes can be attributed to ischemic type, which is caused by thrombi or emboli of blood vessels in the brain, resulting in a sudden interruption of oxygen and glucose as well as subsequent neuronal death and brain damage [2]. Although intravenous thrombolysis with tissue plasminogen activator and mechanical thrombectomy are both currently approved therapeutic strategies for acute ischemic stroke, the therapeutic time window is strictly limited within 4.5 hours for intravenous thrombolysis and at most 24 hours for mechanical thrombectomy after stroke onset, making them unpractical to a large number of stroke patients who are outside the time window [3, 4]. Earlier treatment by shortening the waiting time can bring bigger proportional benefits to stroke patients. Alternatively, targeting the ischemia-induced detrimental events such as destruction of vascular wall, excitotoxicity, programmed cell death and neuroinflammation would be the other potential option to extend the time window and improve stroke prognosis [5, 6].

Netrin-1, the first purified member of the netrin family, originally functioned as a bi-functional guidance cue of repelling or attracting axonal pathfinding depending on its receptor identities [7]. In addition, netrin-1 is also involved in cell migration, synaptic formation and tissue morphogenesis during embryonic development and in the adult brain [8, 9]. Importantly, accumulating evidence has shown that netrin-1 can promote axonal regeneration, synaptic remodeling, neural stem cell migration and white matter repair in different stroke models, with a close association with the regulation of angiogenesis, programmed cell death and neuroinflammation [10-14]. Here, we review previously published articles, including ours, and focus on the implications of netrin-1 and its possible signaling pathways on neuroprotection after ischemic stroke.

2. STRUCTURES AND FUNCTIONS OF NETRIN-1 AND ITS RECEPTORS

The structures of netrin-1 and its receptors are graphically outlined in Fig. (**1**). Netrins are the members of laminin superfamily with highly-conserved structures. As the most characteristic molecule of secreted netrins, netrin-1 is composed of an N-terminal domain VI followed by three epidermal growth factor repeats of domain V, which is similar to the laminin γ chain, plus a positively charged C-terminal

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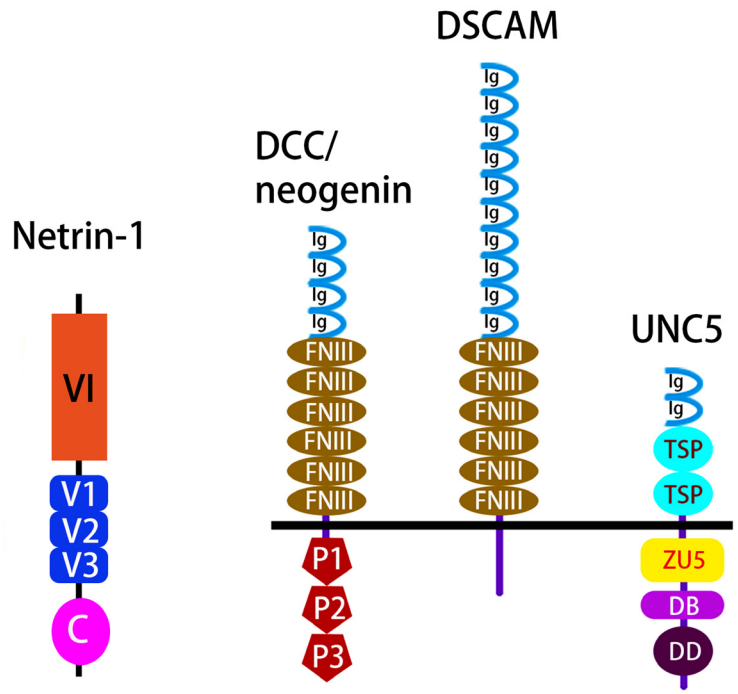

Fig. (1). Structures of netrin-1 and its receptors. Netrin-1 interacts with its receptors DCC/neogenin, DSCAM and UNC5 primarily by N-terminal domain VI and V. The fourth/fifth FNIII repeats of DCC/neogenin or the Ig repeats of UNC5 and DSCAM are supposed sites to bind to netrin-1. Ig, immunoglobin; FNIII, fibronectin III; TSP, thrombospondin; ZU5, homologous to a portion of Zona Occludens; DB, DCC binding domain; DD, death domain. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

domain (also known as the NTR module) being enriched in basic amino acids. Domains VI and V bind to netrin-1 receptors like deleted in colorectal cancer (DCC) and uncoordinated 5 (UNC5) families, while C-domain binds to membrane glycolipids and extracellular matrix components such as heparin sulfate proteoglycans and integrins, serving as crucial sites for the biological function of netrin-1 [15, 16].

Netrin-1 is extensively expressed in the developing and mature mammalian central nervous system, exerting diversely biological functions by engaging its different receptors to regulate signal transduction and cell adhesion [17, 18]. All netrin receptors are transmembrane proteins and belong to the immunoglobin superfamily, mainly including the DCC/neogenin family, the UNC5 family and Down syndrome cell-adhesion molecule (DSCAM). It is generally acknowledged that DCC mediates axon attraction, whereas UNC5 homodimers or UNC5-DCC heterodimers mediate axon repulsion [19, 20]. Importantly, both DCC and UNC5 homologs are dependence receptors, mediating cell death when unbound to their ligand netrin-1, otherwise promoting cell survival when bound to netrin-1 [21, 22]. DSCAM is also proposed to participate in netrin-dependent axon guidance during neural development *via* its immunoglobulin domains [23]. The specific proteins implicated in the functions of netrin-1 remain unclarified, but netrin receptors could function as caspase substrates, and the receptor-mediated cleavage of caspases is required for cell death through multiple cellular signaling pathways, including extracellular signal-regulated kinases (ERKs), death-associated protein kinase (DAPK), phosphoinositide-3-kinase (PI3K) /protein kinase B (AKT), and c-Jun N−terminal kinases (JNKs) [18, 24].

3. NETRIN-1 AND POST-STROKE NEUROPROTECTION

3.1. Angiogenesis

Angiogenesis is a sprouting process of new capillaries from pre-existing blood vessels, involving the proliferation, differentiation and migration of endothelial cells (ECs) as well as degradation of the extracellular matrix by proteolytic enzymes [25, 26]. Blood vessels in the adult brain are usually in a quiescent state but ECs maintain high plasticity. Under pathological conditions, new vessels are formed primarily through angiogenesis [27]. Stroke strengthens the transcription of genes and the synthesis of proteins associated with angiogenesis, with a beneficial role of supplying nutrition to neurons against ischemic insult in an infarcted zone by remodeling collateral circulation [28-30]. Moreover, the newly-formed vessels can act as a scaffold to help post-stroke neurogenesis. Endogenous neuroblasts in the subventricular zone migrate to the infarcted area along the vasculature, and subsequently differentiate into new neurons in local [30, 31]. Taken together, angiogenesis can restore local blood flow and improve neurological recovery after stroke. However, it is not clear whether angiogenesis necessarily gives rise to an intact and functional vessel network in the ischemic zone after stroke. Our previous study showed that although angiogenesis took place in the remote thalamus post cerebral infarction, the function of new-formed vessels seemed to be still imperfect, characterized by increased extravasation of albumin and down-regulation of tight junction protein [32]. Thus, it is necessary to improve post-stroke angiogenesis for better neurological recovery.

Netrin-1 has been proven to present its pro-angiogenic activity in embryonic development dependently on, or independently of its receptors [33, 34]. Netrin-1 facilitated angiogenesis by promoting endothelial proliferation, migration and adhesion towards vascular smooth muscle cells [35], increasing endothelial nitric oxide production *via* DCC-dependent ERKs signaling and endothelial nitric oxide synthase feed-forward mechanism [36], or blocking UNC5B-dependent endothelial apoptosis *via* DAPK signaling [37, 38]. However, in some cases, netrin-1 also acts as an antiangiogenic factor. Lu *et al.* [39] and Larrivee *et al.* [40] demonstrated that netrin-1 decreased endothelial migration and filopodial extension, as a result, suppressed angiogenesis on the condition that UNC5B was expressed. The deletion of the UNC5B gene was able to reverse the netrin-1-mediated suppression of angiogenesis. Whether netrin-1 is a pro- or anti-angiogenic factor needs further investigation [41]. Yang *et al.* [42] showed that the role of netrin-1 to angiogenesis may depend on its concentration: promoting angiogenesis in low doses while inhibiting that in high doses *in vitro*. Consequently, it can be inferred that the contradictory results be attributed to the purity and concentrations of netrin-1 used, and the types of netrin-1 receptors expressed on specific cell types in different experimental settings. Stroke induced the expression of netrin-1 as well as its receptors UNC5B, DCC and neogenin in neurons, glial cells and ECs around the peri-infarct area, indicating a temporal and spatial overlap with axon regeneration and angiogenesis [43, 44]. Further studies revealed that netrin-1 overexpression by delivering adeno-associated viral netrin-1 vector into the brain increased the peri-infarct vessel density and the migration of immature neurons towards the infarct territory, favoring functional recovery post stroke [45, 46]. Our previous study also found that netrin-1 ameliorated the impairment of blood-brain barrier secondary to ischemic stroke by promoting tight junction function and endothelial survival through its UNC5H2 receptor [32]. Altogether, the present data favor that netrin-1 appears to be a pro-angiogenic factor after stroke.

3.2. Neuronal Autophagy

Autophagy, known as type II programmed cell death, is an evolutionarily conserved catabolic mechanism for self-renewal in eukaryotic cells. In the process, cytoplasmic components such as long-lived or misfolded proteins as well as damaged organelles are sequestered into autophagosomes and fused with lysosomes for degradation; then the degraded material is recycled for maintenance of cellular homeostasis [47]. It is believed that multiple complexes of proteins encoded by autophagy-related genes are involved in autophagy induction, pre-autophagosome elongation and autophagosome formation, of which mechanistic target of rapamycin complex-1 is a key negative target by interacting with adenosine 5′-monophosphate-activated protein kinase (AMPK), PI3K/AKT and ERKs signaling pathways [48, 49]. Autophagy is maintained at a low level under normal physiological conditions but can be ignited by either nutrient starvation or metabolic stress. Dysfunction of autophagy has been tightly linked to broad human diseases, including cancer, cardiovascular diseases, neurodegenerative diseases and autoimmune diseases [50, 51]. Meanwhile, autophagy was activated not only in neurons [52-55], but also in microglia [56, 57], astrocytes [58, 59] and ECs [60, 61] in different cerebral ischemia/reperfusion animal models. It is suggested that stroke-induced autophagy exhibits a dual role in neuronal survival depending on the duration of cerebral ischemia and the extent of autophagy activation, as moderate autophagy prevents neuronal injury while over-activation of autophagy causes cell death instead [62]. Thus, an elaborated intervention to autophagy is required for efficient stroke treatment.

Previous studies have implied a potential association between autophagy and netrin-1/UNC5. Autophagy-related kinase UNC-51 and its binding partner UNC-14 guided the subcellular localization of netrin-1 receptor UNC-5 and axonal growth in C. elegans [63, 64]. Noticeably, UNC5H2 could trigger cell death *via* the activation of DAPK, which is a critical regulator of autophagy [65, 66]. The association between autophagy and UNC5 was also confirmed in mechanical injury-induced neuralgia by our group recently, in which UNC5 regulated autophagy influx through phosphorylated UNC51-like kinase [67]. Furthermore, we found that netrin-1 upregulated PI3K-mediated autophagy activity through its UNC5H2 receptor post stroke *in vivo* and upon oxygen-glucose deprivation *in vitro* [32]. Conversely, Tang *et al.* [68] reported that netrin-1 protected cortical neurons against ischemic insult by inhibiting PI3K-mediated autophagy activity using a similar stroke model. The discrepancy could be attributed to the differences in experimental setup. We stressed ECs in the thalamus with an infusion of netrin-1 at 600 ng/d for 7 days *in vivo* and a concentration of netrin-1 at 50 ng/mL *in vitro*, whereas Tang *et al.* observed neurons in the cortex with netrin-1 of 500ng/d for 3 days *in vivo* and 250 ng/mL *in vitro*. As mentioned above, modest autophagy at the early stage of ischemia could be protective against ischemic insult while over-activating or long-term autophagy be detrimental. Therefore, it is not striking that autophagy activity in different kinds of cells is differential in response to a certain concentration of netrin-1. Overall, it seems that netrin-1 can promote cell survival *via* autophagic regulation after ischemic stroke, comparative to the favorable effect of netrin-1 to post-injury repair of myocardium or spinal cord [69, 70]. However, the present results distinctly infer different mechanism from each other, making more studies necessary to explore the details inside. It is also unclear whether other receptors of netrin-1, such as DCC and neogenin, play similar roles in post-stroke autophagic regulation.

3.3. Neuronal Apoptosis

Apoptosis plays a critical role during neural development by eliminating misleading axons and unneeded synaptic connections [71]. Two dominant types of neuronal apoptosis have been already identified hitherto. The intrinsic pathway (also referred to as the mitochondrial pathway) is triggered by damaged mitochondria with the sequential activation of the BH3-only proteins and the pro-apoptotic Bcl-2 family members as well as the inactivation of the anti-apoptotic Bcl-2 family members. Mitochondrial proteins released into the cytosol lead to the formation of apoptosome, which can activate the downstream cascades of caspase-9/caspase-3/proteinase/nuclease. By contrast, the extrinsic pathway (also known as the death receptor pathway) is mediated by hydrolytic cascades of caspase-8/caspase-3 through the death receptors (members of the tumor necrosis factor superfamily) at the cell surface. Whatever intrinsic or extrinsic pathway is

Table 1. The speculated role of netrin-1 in post-stroke neuroprotection.

Targets	Receptors Involved	Associated Signaling Pathway
Pro-angiogenesis		
Promote tight junction function and endothelial survival [32]	UNC5H2	PI3K
Autophagy		
Upregulate endothelial autophagy [32]	UNC5H2	PI3K
Downregulate neuronal autophagy [68]	------	PI3K/mTOR
Apoptosis		
Attenuate secondary neuron apoptosis [83]	UNC5H2	------
Inhibit endoplasmic reticulum stress and neuron apoptosis [84-86]	DCC	ERKs
Promote synaptic formation, axonal regeneration and reduce infarcted size probably through inhibiting apoptosis [87, 88]	DCC	JNK1, Notch1
Neuroinflammation		
Reduce pro-inflammatory cytokines [112]	UNC5H2	PI3K/AKT

------, unknown.

activated, they undoubtedly destruct the cell with a morphological characteristic of chromatin condensation and DNA fragmentation [72, 73]. After stroke onset, both apoptosis pathways can be aroused and progressed at least days to weeks. Generally, immediate neuronal death occurs in the ischemic core mostly through necrosis, the process of which is irreversible and cannot be prevented. On the other hand, apoptosis prevails in the ischemic penumbra around the ischemic core with a slower development, which can be efficiently prohibited for neuronal survival and neurological recovery. Suppression of apoptosis has been proposed as a potential strategy to salvage ischemic brain tissue in the penumbra [6, 74, 75].

The DCC and UNC5 homologs are referred to as dependence receptors, both inducing apoptosis in the absence of their ligand netrin-1. On the other hand, the binding of netrin-1 to these receptors switches a pro-apoptotic signaling to a pro-survival signaling [76]. DCC and UNC5H are both caspase substrates, the proteolytic cleavage of whose intercellular domains by activated caspases inevitably facilitates caspase-dependent apoptosis (*e.g.* p53-induced apoptosis, activation of DAPK, and transactivation of proapoptotic target genes) [65, 77-81]. In the presence of netrin-1, the anti-apoptotic role is achieved by changing the conformation of netrin-1 receptors, blocking caspase-dependent cleavage or reinforcing anti-apoptotic signaling such as ERKs and AKT [82]. Netrin-1 has been shown to exert its neuroprotective effect through diverse anti-apoptotic pathways after ischemic stroke. We previously reported that UNC5H2 was predominantly up-regulated and was related to neuron loss in the ipsilateral thalamus after cerebral ischemia. Netrin-1 could rescue neuron loss by attenuating secondary apoptosis, probably *via* its UNC5H2 receptor [83]. In addition, recent studies found that netrin-1 inhibited endoplasmic reticulum stress and neuron apoptosis through DCC-mediated phosphorylation of ERKs after ischemic insult *in vivo* and *in vitro* [84-86]. Other signaling pathways associated with apoptosis have also been explored. The JNKs, defined as important signaling effectors of cell death by phosphorylating the downstream proteins, play an essential role in activating the intrinsic apoptosis pathway in neurons. Zheng *et al.* [87] discovered that netrin-1, in the coordination of DCC, promoted synaptic formation and axonal regeneration by increasing the activity of phosphorylated JNK1 after ischemic stroke. Meanwhile, Yang *et al.* [88] reported that netrin-1 reduced infarction volume through inhibiting Notch1, a signaling pathway resulting in cell vulnerability to apoptosis. Therefore, a strategy of anti-apoptosis by netrin-1 could be really feasible in stroke therapy.

3.4. Neuroinflammation

Post-stroke inflammation is characterized by the activation of microglia and astrocytes as well as the production of cytokines and chemokines at the early stage, followed by the infiltration of blood-derived neutrophils, monocytes/ macrophages and lymphocytes into the ischemic brain for days to weeks [89, 90]. Post-stroke inflammation is prompted by complicated signaling pathways. Typically, toll-like receptors, NACHT, LRR and PYD domains-containing protein 3, mitogen-activated protein kinases and nuclear factor-kappa B (NF-κB) are known major components in both innate and adaptive immunity post ischemia, the activation of which can induce differentiated inflammatory responses by adjusting pro-inflammatory mediators including tumor necrosis factors, interleukins (IL-1 and IL-6), as well as anti-inflammatory mediators, including IL-10, transforming growth factor β and insulin-like growth factor 1 [91-94]. The exact significance of post-ischemic inflammation is largely under discussion. Heretofore, the attempts of single anti-inflammatory treatment have been proven unsuccessful in clinical translation, although it was effective in animal models [95, 96]. Growing evidence shows that inhibition of inflammation could attenuate brain injury and neurological impairment at the acute stage; nonetheless, it could also retard neural regeneration and long-term functional prognosis [97-99]. It seems that the dual functions could depend on the time period and extent of inflammation after ischemia; that is, early or excessive activation is disadvantageous, but later or moderate activation is beneficial. Obviously, a more delicate tactic for inflammatory regulation after ischemic stroke can serve as a basis of effective treatment in the clinic.

Previous studies demonstrated that netrin-1 expressed on vascular or mucosal endothelium can be regulated by inflammatory conditions such as infection or hypoxia, where netrin-1 acted as a potent inhibitor of leukocytic transepithelial migration in response to chemotactic stimuli by engaging its UNC5 receptor or possible A2B adenosine receptor [100-102]. Furthermore, the anti-inflammatory property of netrin-1 was reported in different disease models, probably involving polarization of macrophage [103], activation of cyclic AMP/protein kinase A [104] and ERK1/2/ endothelial nitric oxide synthase signaling pathway [105], or inhibition of NF-κB signaling pathway [106]. However, the direct evidence of netrin-1 on post-stroke inflammation is relatively limited. Guo *et al.* [107] discovered that upregulated netrin-1 at the acute phase was associated with neurological recovery at 3 months after ischemic stroke and might be a potential prognostic biomarker, the mechanism of which was speculated as to the anti-inflammatory property of netrin-1. The phenotypic transformation of M1/M2 microglia and A1/A2 astrocytes has been proven to play a vital role in neuroinflammation [108, 109]. Our group and others found that hypoxic and ischemic stimuli caused an increase of M1-like polarization of microglia and reactive gliosis, contributing to neuronal death and tissue repair [110, 111]. In addition, He *et al.* [112] revealed that netrin-1 reduced the release of pro-inflammatory IL-1β and IL-12β in lipopolysaccharide-stimulated astrocytes and after ischemic stroke *via* its UNC5H2 receptor. Activated astrocytes were inhibited by netrin-1 *via* PI3K/AKT signaling pathway with the involvement of nuclear transcription factor peroxisome proliferator-activated receptor gamma. Taken together, these studies infer that netrin-1 may regulate the functions of microglia and astrocytes in neuroinflammation, nonetheless, much more studies are needed to clarify the implications.

CONCLUSION

Several lines of evidence demonstrate that neuronal death, mainly caused by vascular impairment, apoptosis, autophagy or neuroinflammation, is associated with increased stroke severity and is an important determinant of stroke prognosis. Obviously, pharmacological interventions to neuronal death are required with the development of multi-target and multi-link instead single-target neuroprotective drugs. To date, there has been certain evidence to support the neuroprotective function of netrin-1 by regulating angiogenesis, autophagy, apoptosis and neuroinflammation after stroke (Table **1**). It is reasonable to speculate that netrin-1 may be a promising drug candidate in reducing stroke severity and improving outcomes. More studies with *in vivo* stroke models are urgently needed to fully elucidate the neuroprotective mechanisms of netrin-1 for effective clinical transformation, and an optimizing scheme combining netrin-1 concentration with its receptor identities has to be further explored to get the best possible benefit post stroke.

LIST OF ABBREVIATIONS

DCC = Deleted in Colorectal Cancer

UNC5 = Uncoordinated 5

DSCAM = Down Syndrome Cell-adhesion Molecule

ERKs = Extracellular Signal-Regulated Kinases

DAPK = Death-Associated Protein Kinase

PI3K = Phosphoinositide-3-Kinase

AKT = Protein Kinase B

JNKs = c-Jun N−terminal Kinases

ECs = Endothelial Cells

AMPK = Adenosine 5′-Monophosphate-activated Protein Kinase

NF-κB = Nuclear Factor-kappa B

ILs = Interleukins

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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