

Shaping the brain vasculature in development and disease in the single-cell era

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	Sprouting angiogenesis	Vasculogenesis	Intussusception	Vessel co-option	Vascular mimicry	Stem cell to EC/PVC /vSMC transdifferentiation
Modes of neovascularization during brain development						
Embryological brain development	Yes, VEGF-A ¹ , Ang-1 ² , Integrin β_8 and α_v^3 , Wnt7a-b/ β -Catenin ⁴ , TGF- β^5 , PPIL4/JMJD6/Wnt ⁶	Yes, PNVP formation, VEGF-A ¹	?	?	?	?
Postnatal brain development	Yes, VEGF-A ^{7,8} , Nogo-A ⁹ , Semaphorin-3A/3E-Plexin D1 ^{10,11} , Slit2-Robo ^{4,12,13}	Yes, VEGF-A ¹⁴	?	?	?	?
Modes of neovascularization in glial brain tumors						
Primary glial brain tumors	Yes, VEGF, Dll4/Notch ¹⁵ , PGC-1 α ¹⁶ , Ephrin B2 ¹⁷ , CXCR4/SDF1 α ¹⁸ , Integrin $\alpha_3\beta_1$ and $\alpha_v\beta_3$ ^{3,19,20}	Yes, BMDCs (EPCs express CXCR4 ^{21,22} , ANG-2/TIE-2 ²³)	Yes, VEGF ²⁴	Yes, ANG-2/Tie-2 ^{25,26} , VEGF ²⁵ , Bradykinin ²⁷ , CXCR4/SDF1 α ^{28,29} , EGFRvIII ³⁰ , MDGI/FA BP3 ^{31,32} , Olig2/Wnt 7a ³³ , CDC42 ³⁴	Yes ³⁵⁻³⁷ , IGFB2 ³⁸ , LRIG1/E GFR ³⁹ , MMP2/MMP14/PI3K-ERK ^{40,41} , ZRANB2 ⁴² , ObR ⁴³	Yes, GSC to EC (Notch and TGF β pathways) ⁴⁴⁻⁴⁸ , GSC to pericyte (Notch1) ^{49,50} , and GSC to vSMC phenotype (BMP4/S MAD) ⁵¹
Modes of neovascularization in brain arteriovenous malformations						
Sporadic brain AVM	Yes, ALK1 ⁵² , ENG ⁵² , ITGB8 ^{53,54} , IL1B ⁵⁵ , GNAQ ⁵⁶⁻⁵⁸ , EPHB4 ⁵⁹ , ANGPTL4 ⁶⁰ , VEGF ⁶¹ , MMP3 ⁶² , MMP9 ⁶³ , Sox17 ⁶⁰ , RBBP8 ⁶⁰ , CDKN2a/b ⁶⁴ , KRAS ⁶⁵⁻⁶⁷	Yes, CD133, SDF-1a, and CD68-positive cells (EPCs) in nidus ⁶⁸	?	?	?	?
Hereditary brain AVM	Yes, ENG ⁶⁹⁻⁷¹ (HHT type I), ALK1 ^{72,73} (HHT type II), TGF β /SMAD pathway,	Yes, CD133, SDF-1a, and CD68-positive cells in nidus (EPCs) ⁶⁸	?	?	?	?

	RASA1 ^{74,75}				
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Table 1. Modes of neovascularization during brain development, in glial brain tumors and in brain AVMs.

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	Signaling pathways	Brain/Retina/Spinal Cord Angiogenesis	Non-CNS Angiogenesis	CNS-specificity	References
Sprouting angiogenesis during brain development					
Embryological brain development	VEGF-A/B/C – VEGFR1/2/3	Yes	Yes	No	1-4
	FGF-2 – FGFR	Yes	Yes	No	5,6
	Ang1 – Tie2	Yes	Yes	No	7-9
	Slit-2 – Robo-4	Yes	Yes	No	10-13
	Semaphorin-3A – Plexin-D1	Yes	Yes	No	14-17
	Semaphorin-3E – Plexin-D1	Yes	Yes	No	18-20
	Ephrin B2 – Eph B4	Yes	Yes	No	21-23
	Netrin-1 – Unc-5b	Yes	Yes	No	24-26
	Netrin-4 – Neogenin (recruitment of Unc-5b)	Yes	Yes	No	25,27,28
	Integrin $\alpha_v\beta_8$ – TGF β R1	Yes	Yes	No	29-32
	Wnt7 – Fzd/Gpr124/Reck	Yes (brain)	No	Yes	33-39
	Norrin – Fzd4/Lrp5/Tspan12	Yes (retina)	No	Yes	40-42
	Netrin-1/Unc5B – Wnt7a/b/Lrp5	Yes	No	Yes	43
	UL – DR6/TROY	Yes	No	Yes	44
	PPIL4 – JMJD6/Wnt	Yes	No	Yes	45
Postnatal brain development	VEGF-A/B/C – VEGFR1/2/3	Yes	Yes	No	1,2
	FGF-2 – FGFR	Yes	Yes	No	5,6
	Ang1 – Tie2	Yes	Yes	No	46
	Nogo-A-S1PR2?	Yes	?	?	47,48
	Nogo-B-NgBR	?	Yes	No	49-51
	Semaphorin-3A – Nrp1/Plexin-D1	Yes	?	?	14,52,53
	Semaphorin-3E – Plexin-D1	Yes	?	?	18,20
	Slit-2 – Robo-4	Yes	Yes	No	10
	Ephrin B2 – Eph B4	Yes	Yes	No	21-23
	Netrin-1 – Unc-5b	Yes	Yes	No	24
	UL – DR6/TROY	Yes	No	Yes	44
	Norrin – Fzd4/Lrp5/Tspan12	Yes	No	Yes	40-42

Sprouting angiogenesis in glial brain tumors					
Glial brain tumors	VEGF-A – VEGFR	Yes	Yes	No	54,55
	FGF-1/2 – FGFR	Yes	Yes	No	56,57
	Dll4 – Notch	Yes	Yes	No	58-60
	Jagged-1 – Notch	Yes	Yes	No	59,60
	PDGF-PDGFR	Yes	Yes	No	61
	EGFL7– Notch	Yes	Yes	No	62
	Ang-2 – Tie-1/2	Yes	Yes	No	63-65
	Slit-2 – Robo-4	Yes	Yes	No	66
	Ephrin B2 – EphB4	Yes	Yes	No	22,67
	Netrin-1– UNC-5b	Yes	?	?	68-70
	Sema3 – Plexin	Yes	Yes	No	71-73
	Integrin $\alpha_v\beta_8$ – TGF β R1	Yes	Yes	No	74
	Integrin $\alpha_v\beta_3$ – TGF β R1	Yes	Yes	No	75,76
	Integrin $\alpha_v\beta_5$ – TGF β R1	Yes	Yes	No	76
	Integrin $\alpha_5\beta_1$ – TGF β R1	Yes	Yes	No	77
	Integrin $\alpha_7\beta_1$ – TGF β R1	Yes	Yes	No	78
	Integrin $\alpha_5\beta_1$ – EGFL7	Yes	Yes	No	77,79
	CXCR4 – CXCL12/SDF1 α	Yes	Yes	No	80
	Wnt1 (anti-angiogenic) & Dkk1 (Wnt inhibitor)	Yes	Yes	No	81
Sprouting angiogenesis in brain arteriovenous malformations					
Hereditary brain AVMs	Endoglin – TGF β R	Yes	Yes	No	82
	TGF β – ALK1	Yes	Yes	No	83
	RASA1 – EPHB4	Yes	Yes	No	84-86
Sporadic brain AVMs	VEGF-A	Yes	Yes	No	87
	TGF β – ALK1 (ACVRL1)	Yes	Yes	No	88-90
	Endoglin – TGF β R	Yes	Yes	No	88
	GNAQ	Yes	Yes	No	91
	Ephrin B2 – EphB4	Yes	Yes	No	92
	K-RAS	Yes	Yes	No	93-95
	IL1B – IL1R	Yes	Yes	No	83
	IL6	Yes	Yes	No	96
	Integrin $\alpha_v\beta_8$ – TGF β R	Yes	Yes	No	97

	ANGPTL4	Yes	Yes	No	98,99
	Wnt7 – Fzd/Gpr124/Reck	Yes	Yes	No	100
	MMP3	Yes	Yes	No	101
	MMP9	Yes	Yes	No	102
	CDKN2a/b (ANRIL)	Yes	Yes	No	103,104
	Sox17	Yes	Yes	No	105
	RBBP8	Yes	Yes	No	105

Table 2. General and CNS-specific molecular mechanisms of angiogenesis during brain development, in glial brain tumors, and in brain AVMs.

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