

Supplementary Information (S.I.)

Title: Microphysiological ischemic stroke model for systematic evaluation of neurorestorative potential of stem cell therapy

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Fig. S13. GFP transfection efficiency

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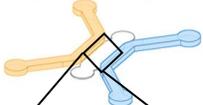
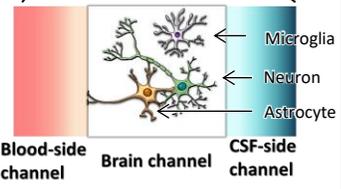
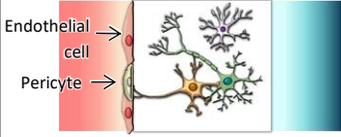
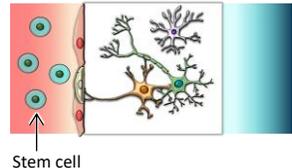
Fig. S15. Fluorescent images showing the expression of stem cell markers in 2D culture before the transplantation

Table S2. Functional characteristics and relevant references of the genes in **Figure 2, 3, and 4.**

Table S3. Functional characteristics and relevant references of the genes in **Figure 5.**

References for the gene information (1-388)

Table S1. Workflow for the sample preparation

		Cell component		Culture condition			
				blood-side channel	CSF-side channel	O ₂ concentration	Flow
	Day 0	Add NPC, astrocytes and microglia (8:4:1) with hydrogel into the 'brain' channel.		Add the mixture of NEM, AM and ACM (8:4:1, v/v/v) – serum free	Add the mixture of NEM, AM and ACM (8:4:1, v/v/v)	20%	No
Neuronal differentiation	Day 3			Add the mixture of NDM, AM and ACM (8:4:1, v/v/v)	Add the mixture of NDM, AM and ACM (8:4:1, v/v/v)	20%	No
BBB construction	Day 5	Add BMEC and pericytes (9:1) into the 'blood-side' channel.		Add the mixture of ECM and PM (9:1, v/v) - 4.7% (v/v) serum	Add the mixture of NDM, AM and ACM (8:4:1, v/v/v)	20%	Yes
Ischemia induction	Day 10			Add glucose/serum-free DMEM	Add glucose/serum-free DMEM	2%	No
Reperfusion and stem cell transplantation	Day 11	Add stem cells into the 'blood-side' channel.		Add the mixture of ECM and PM (9:1, v/v)	Add the mixture of NDM, AM, and ACM (8:4:1, v/v/v)	20%	Yes
	Day 18	Lyse the whole tissue for analysis.					

Abbreviation: NPC: Neural progenitor cell, NEM: Neural expansion medium, AM: Serum-free Astrocyte medium, ACM: Astrocyte-conditioned medium, NDM: Neural differentiation medium, ECM: Endothelial cell medium, PM: Pericyte medium.

Fig. S1.

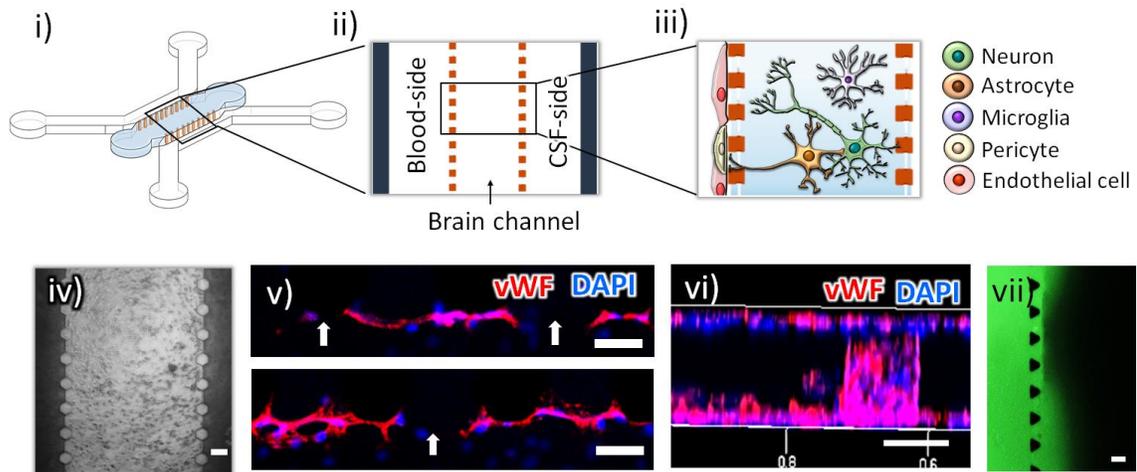


Figure S1. Endothelium defects in a chip with micro-poles. (i-iii) Chip design with micro-poles. The schematic illustration of the chip design w/ micro-poles (i-ii) and the spatial distribution of the NVU constituent cells in the chip (iii). (iv) A phase contrast image showing the hydrogel deployed in the 'brain' channel. (v-vi) Single layers (v) and a reconstructed side view (vi) of confocal microscopic images showing the endothelium (stained 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 .

Fig. S2.

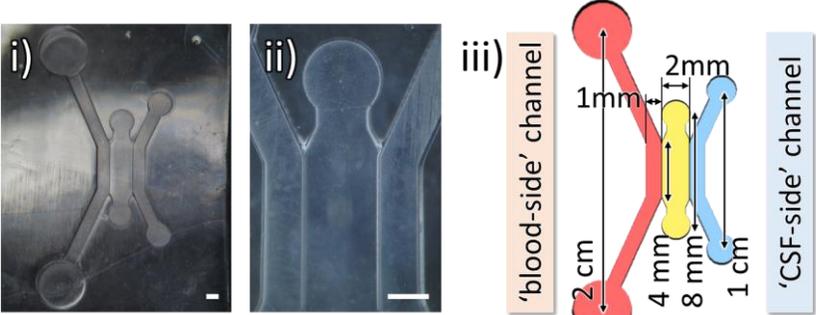
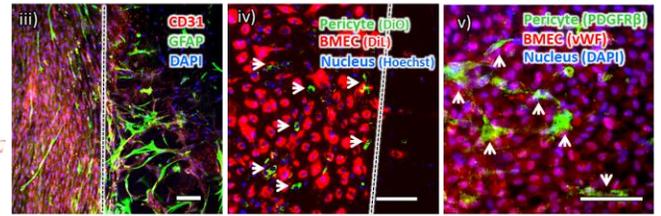
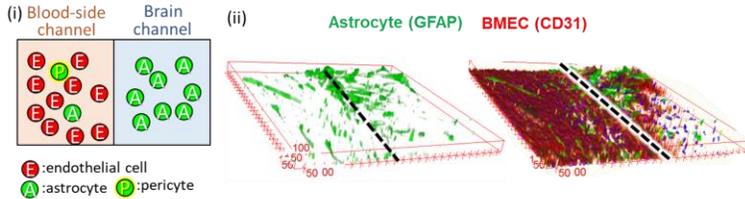


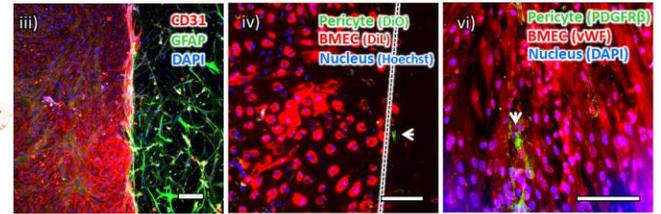
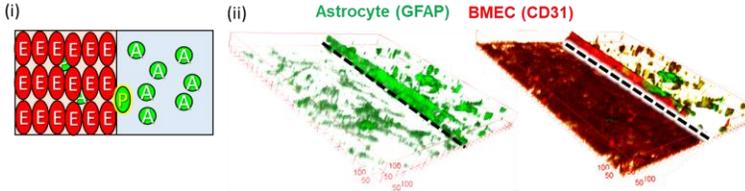
Figure S2 A master mold prepared by a 3D printer (i), PDMS replica (ii), and its dimensions (iii). Scale bars: 1 mm.

Fig. S3.

A. Immature endothelium



B. Mature endothelium



C. Spatial cell distribution in the chip

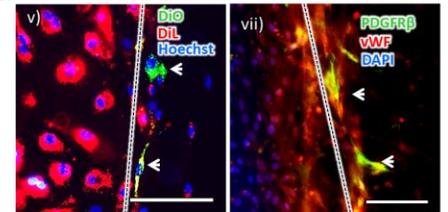
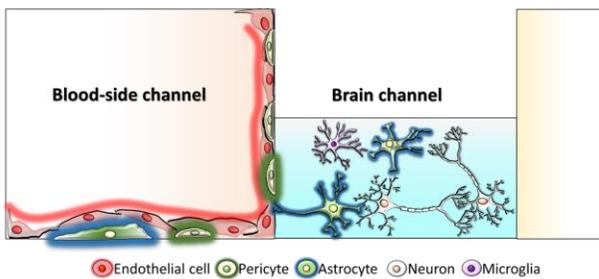


Figure S3. Spatial cell distribution in our chip. A. Immature endothelium. (i) A schematic diagram of the top view of the cell distribution. **(ii) & (iii)** Astrocytes (stained as green by GFAP) are exposed among the endothelial cells (stained as red by CD31) and clearly visible. **(iv)** Pericytes (pre-stained as green by DiO) show similar pattern and are clearly visible among the endothelial cells (pre-stained as red with DiI). White arrows indicate the pericytes. **(v)** Pericytes were immuno-stained by a pericyte marker, PDGFR β . **B. Mature endothelium. (i)** A schematic diagram of the top view of the cell distribution. **(ii) & (iii)** Astrocytes (stained as green by GFAP) are covered by the mature endothelium (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 DiI). **(vi-vii)** Pericytes were immuno-stained by a pericyte marker, PDGFR β . Only a few pericytes are exposed between 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 μ m.

Fig. S4.

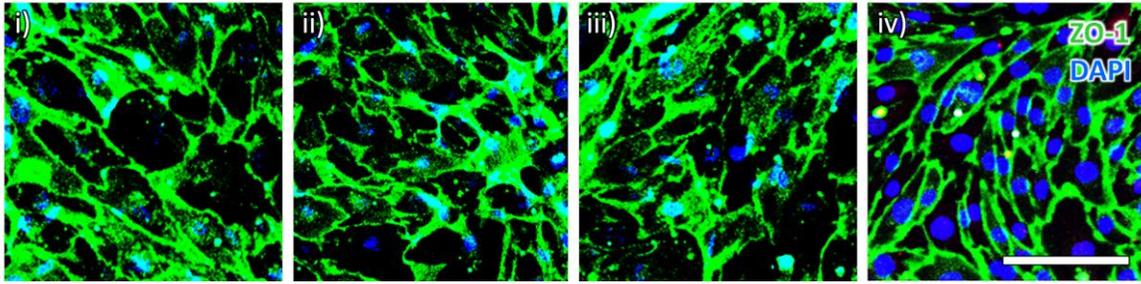


Figure S4. Morphological changes of hBMEC due to the interaction with glial cells. Fluorescence images showing the morphology of hBMEC when they were cultured alone (i), co-cultured with pericytes (ii), astrocytes (iii), or both pericytes and astrocytes (iv). Normal morphology of hBMECs was observed 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 μ m.

Fig. S5.

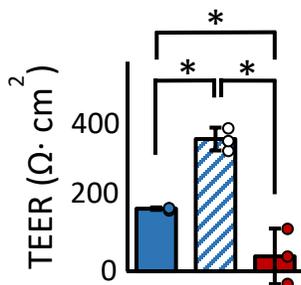


Figure S5. TEER values measured with DC. The TEER value of BBB significantly increases in the presence of flow compared to the cells in a static culture (n=3). Statistical significance is denoted as ‘*’.

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[†]. 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 with a DC resistance meter. The TEER across the endothelium was calculated according to the equation below:

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

, 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, possibly due to the cytotoxicity of DC[‡]. 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).

[†]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).

[‡]Srinivasan, B. *et al.* TEER measurement techniques for in vitro barrier model systems. *Journal of laboratory automation* **20**, 107-126 (2015).

Fig. S6.

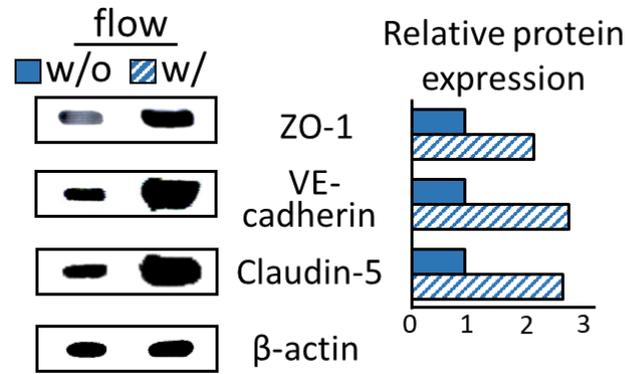


Fig. S6. Expression changes of BBB markers by flow. Western blots showing the expression levels of the BBB markers, ZO-1, VE-cadherin, and Claudin-5. The expression levels were measured with the cell lysates of four samples at each condition.

Method for Western blot analysis

To analyze the protein expression level with western blotting, 20 μ L of lysis buffer (radio-immunoprecipitation assay (RIPA) buffer (Sigma Aldrich Cat. No.: R0278) + 0.5 mM EDTA + 1 \times 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 $^{\circ}$ 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 \times TBST (Tris buffered saline + 0.1% Tween 20) with 5% BSA and then incubated with primary antibodies overnight at 4 $^{\circ}$ C followed by three washes with 1 \times 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 \times 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.

Fig. S7.

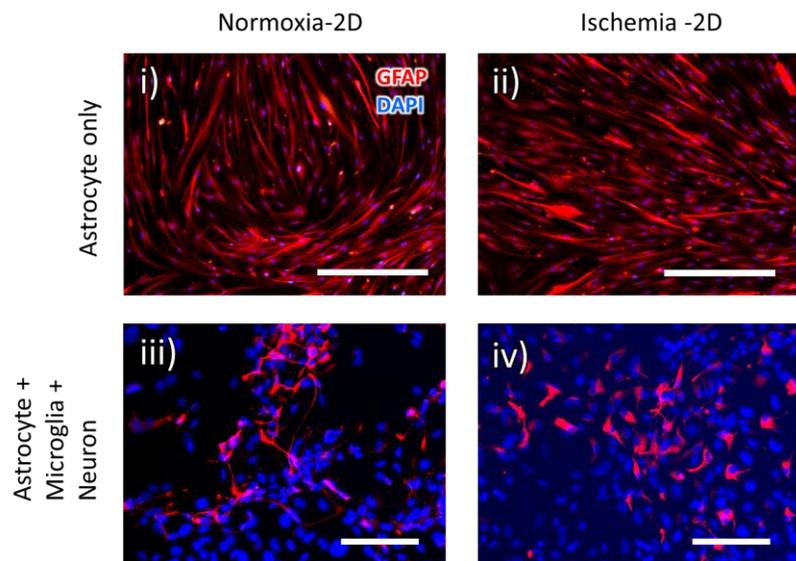


Figure S7. The expression of an astrocyte marker, Glial Fibrillary Acidic Protein (GFAP) in the astrocytes cultured in traditional 2D culture plates. The astrocytes were cultured alone (**i & ii**) or co-cultured with microglia and neurons (**iii & iv**) under normoxia (**i & iii**) or ischemia (**ii & iv**) conditions. Scale bars: 200 μm .

Fig. S8.

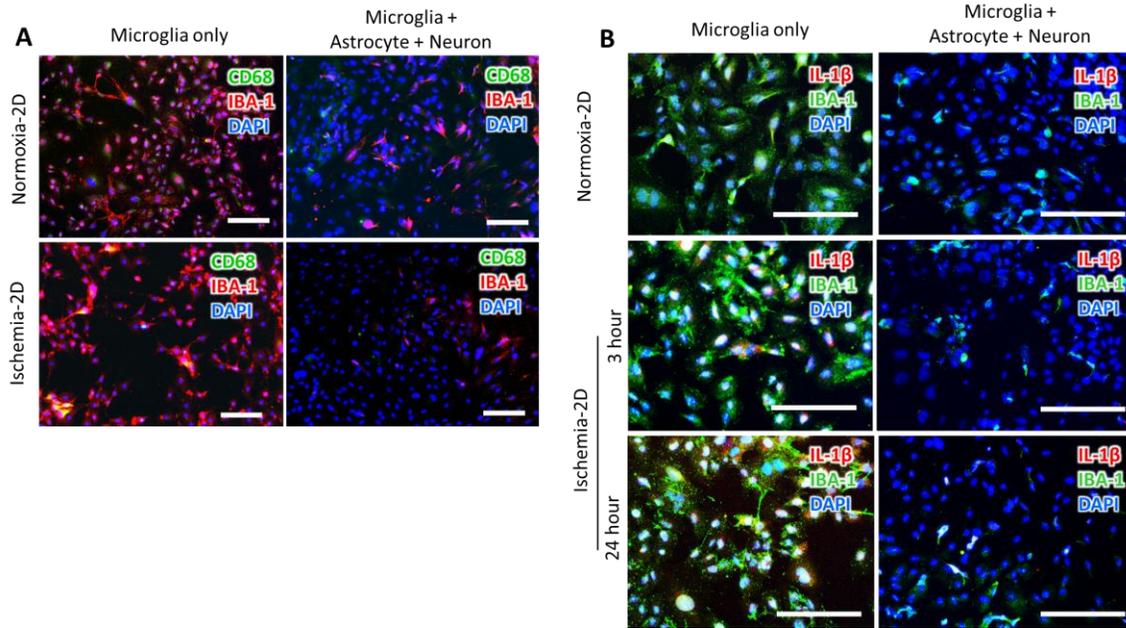


Figure S8. Microglia behavior in traditional 2D cultures. Microglia were immunostained by its specific marker, IBA-1, and pro-inflammatory microglia markers, CD68 (A) or IL-1 β (B). Scale bars: 200 μ m.

Fig. S9.

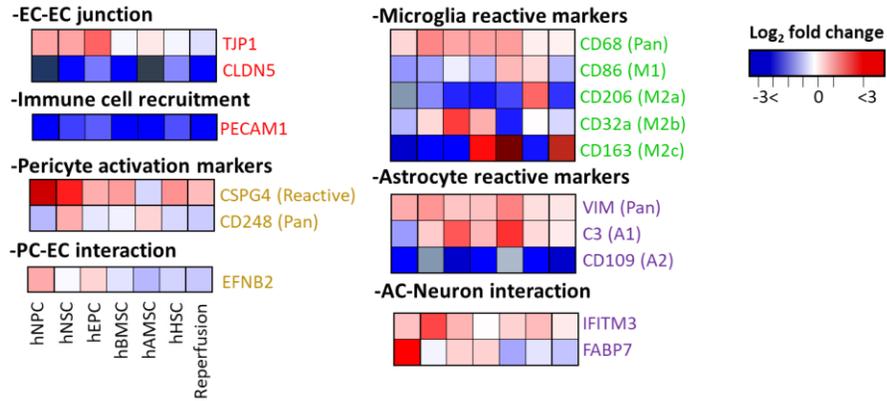


Figure S9. Gene expression alteration of gliosis phenotype markers by transplanted stem cells and reperfusion. Magnified heatmap of **Figure 5A i**. The gene lists colored in red, yellow, green and purple are the phenotype markers of endothelial cells, pericytes, microglia and astrocytes, respectively.

Fig. S10.

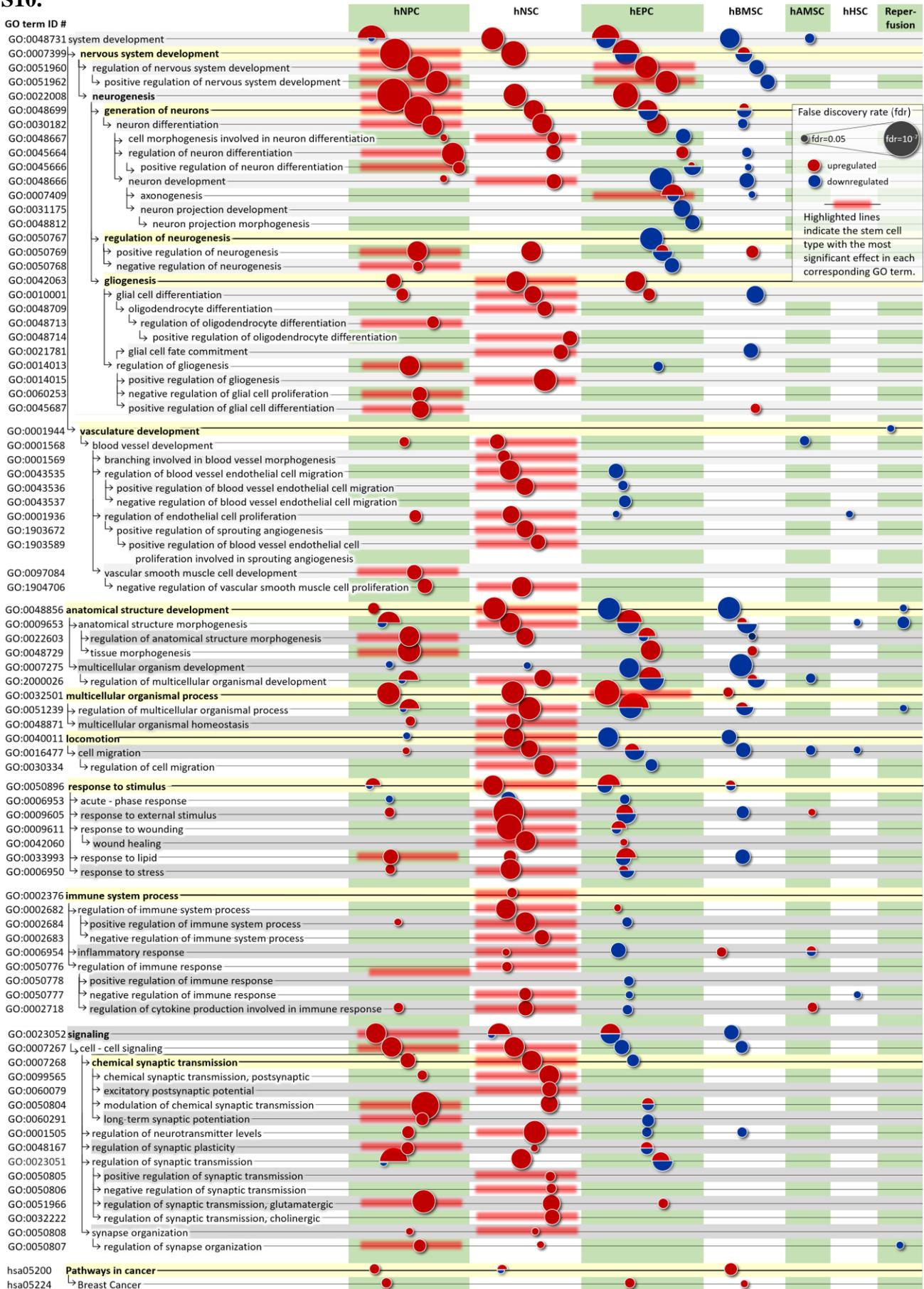


Figure S10. GO terms from the functional enrichment analysis on the genes with over 4-fold expression changes.

Fig. S11.

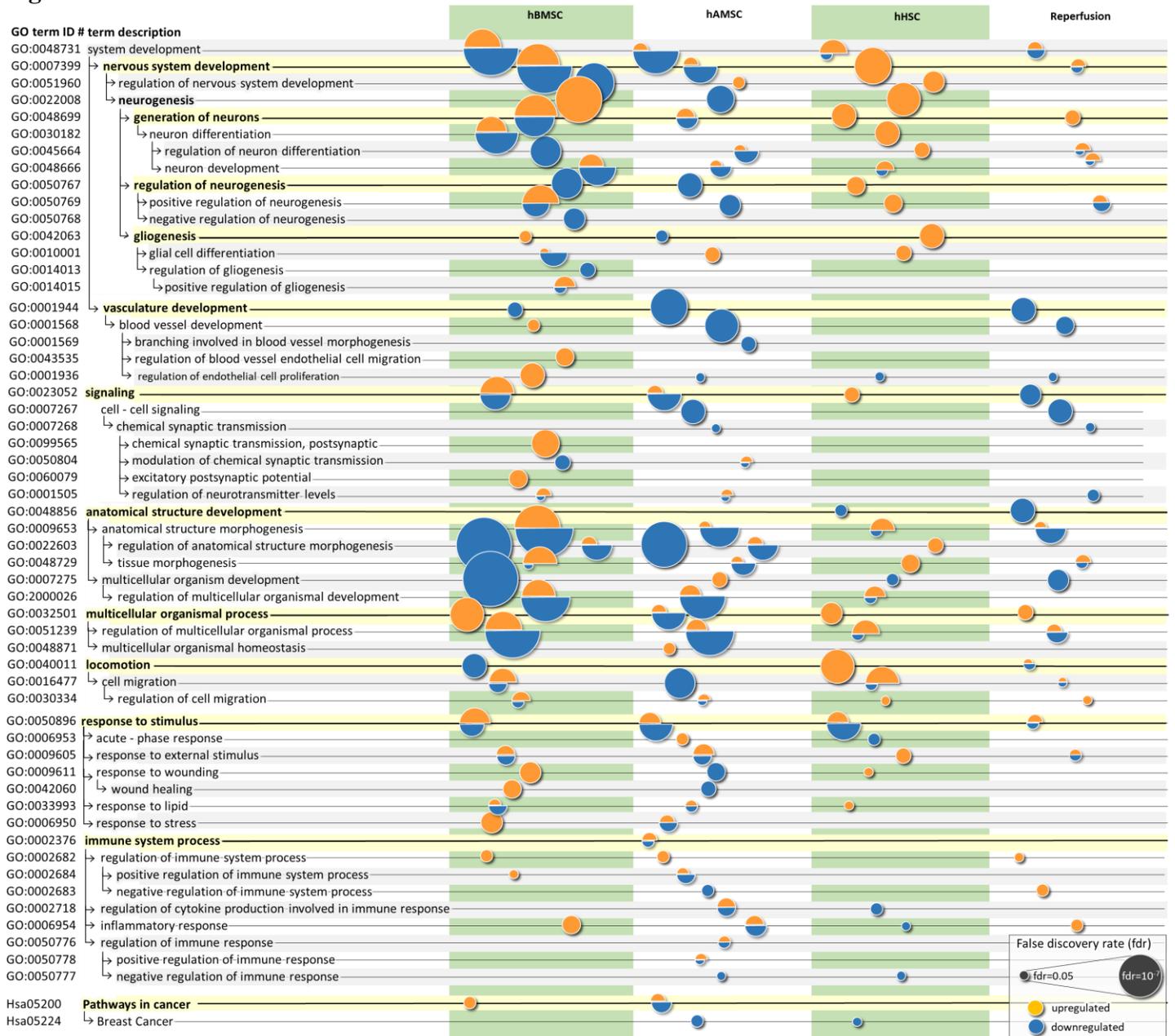


Figure S11. GO terms from the functional enrichment analysis on the genes with over 2-fold expression changes.

Fig. S12.

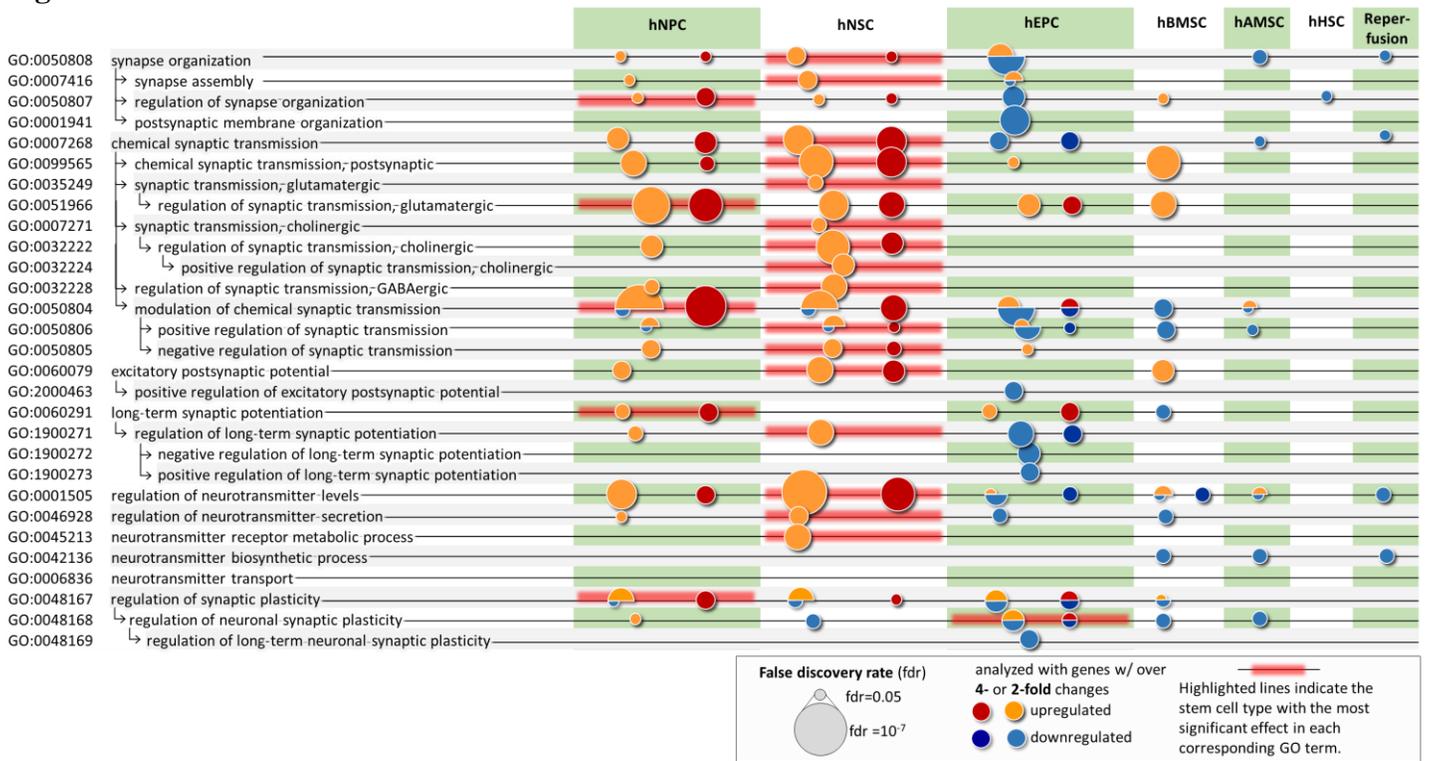


Figure S12. GO terms related to synapse and neurotransmitters, from the functional enrichment analysis on the genes with over 4- and 2-fold expression changes. The lines highlighted in red indicate the stem cell type most influential for each GO term.

Figure S13.

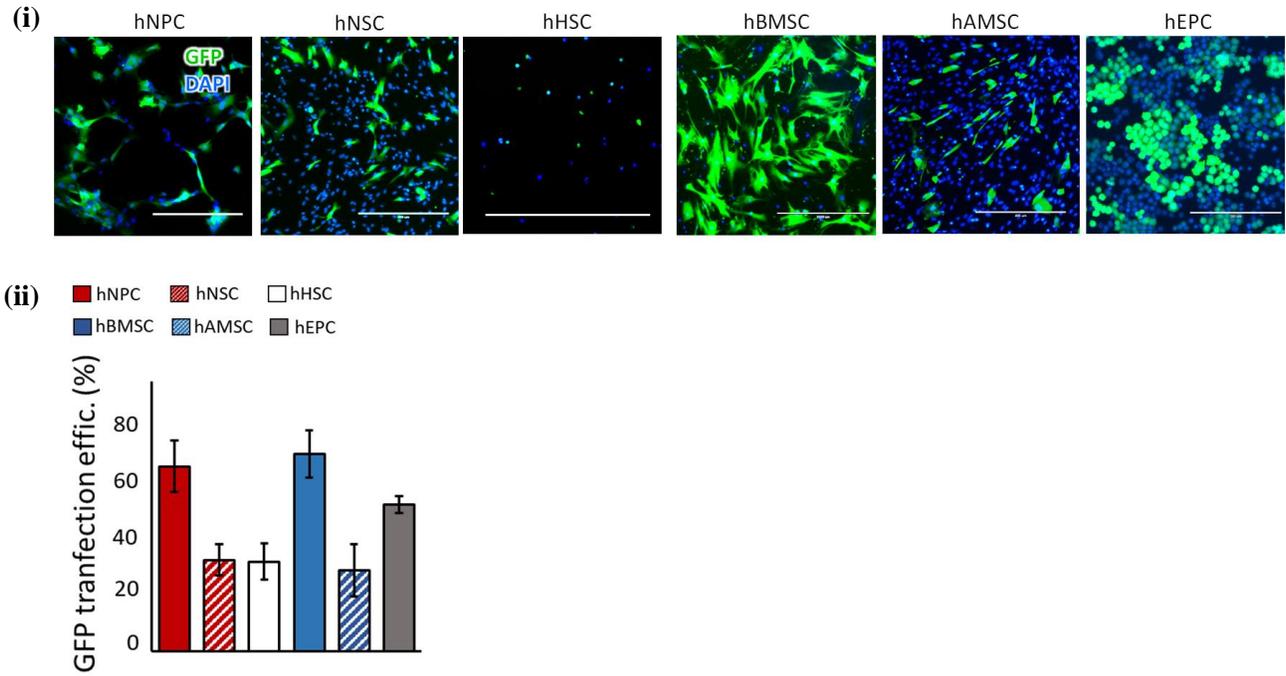


Fig. S13. GFP transfection efficiency of each stem cell type. (i) Images of the Green Fluorescent Protein (GFP)-expressing stem cells taken 3 days after adding GFP Lentiviral Vectors. Scale bars: 400 μm . **(ii)** GFP transfection efficiency was calculated by taking the ratio of the numbers of GFP-expressing cells over the overall cell numbers.

Fig. S14.

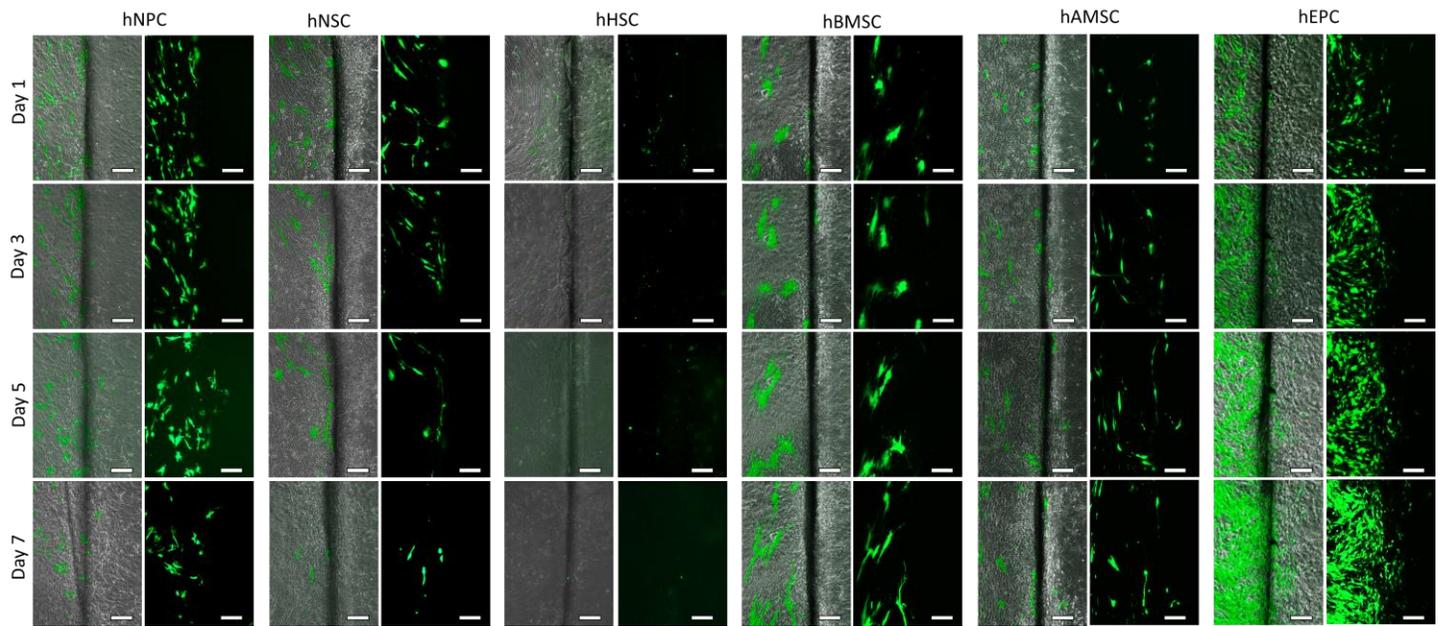


Figure S14. Time-lapse images of GFP-expressing stem cells invading across the BBB on a chip. Left-side panels in each stem cell type show the merged images of the phase contrast image and the fluorescent image. Right-side panels show the fluorescent images alone. Scale bars: 200 μm

Fig. S15.

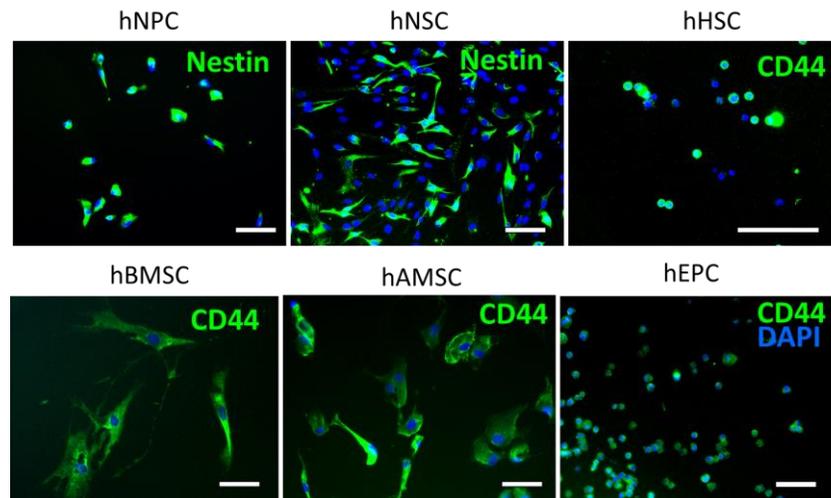


Figure S15. Fluorescent images showing the expression of stem cell markers in 2D culture before the transplantation. Scale bars: 100 μ m

Table S2. Functional characteristics and relevant references of the genes in **Figure 2, 3, and 4.**

Apoptosis	RIPK2	Receptor interacting serine/threonine kinase 2	<ul style="list-style-type: none"> - Encodes a potent activator of NF-Kb and inducer of apoptosis. - The expression of RIPK2 is significantly elevated after ischemic stroke ¹.
	PSMB8	Proteasome subunit beta 8	<ul style="list-style-type: none"> - Encodes $\beta 5i$ 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 ischemic stroke. It increases infarction volume and promotes inflammatory reaction ³.
	HSPB1	Heat shock protein family B (small) member 1	<ul style="list-style-type: none"> - HSPB1 is strongly induced during the stress response such as ischemia. It has powerful neuroprotective effects, increasing the survival of cells subjected to cytotoxic stimuli ⁴.
	GADD45B	Growth arrest and DNA damage inducible beta	<ul style="list-style-type: none"> - This gene is an important factor in DNA repair, apoptosis, cell survival, and growth arrest. - GADD45B expression is significantly increased in ischemic brain ⁵. Knockout of GADD45B significantly increases neuronal apoptosis ⁶.
	MCL1	MCL1 apoptosis regulator, BCL2 family member	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Encodes a protein that belongs to a family of apoptotic suppressor proteins. - XIAP expression increases after focal cerebral ischemia ⁸.
Redox	HMOX1	Heme oxygenase 1	<ul style="list-style-type: none"> - Heme oxygenase is an essential antioxidant enzyme in heme catabolism and it acts as stress defense. - Ischemic stroke strongly upregulates HMOX1 expression ⁹.
	TXNIP	Thioredoxin interacting protein	<ul style="list-style-type: none"> - 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 ischemia strongly increases TXNIP expression. TXNIP activation is a key event linking oxidative stress to inflammation and apoptosis in neurons ¹⁰.

		TXNRD1	Thioredoxin reductase 1	<ul style="list-style-type: none"> - 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 ischemic stroke ¹¹.
		SOD2	Superoxide dismutase 2	<ul style="list-style-type: none"> - 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. - Ischemia induces the expression of SOD2. SOD2-deficient mice presents higher levels of oxidative stress after ischemic stroke ¹².
Trophic factors		IGFR2 (FCGR2 A)	Fc fragment of IgG receptor IIa	<ul style="list-style-type: none"> - 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 (FCGR1 A)	Fc fragment of IgG receptor Ia	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 ischemic stroke ¹⁸.
		VEGFA	Vascular endothelial growth factor A	<ul style="list-style-type: none"> - 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 ischemic stroke ²¹.
		VEGFR2 (KDR)	kinase insert domain receptor	<ul style="list-style-type: none"> - 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 ischemic 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 ischemia 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 . - Ischemic 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 ischemia-induced neuronal death ²⁶ . - TGFB1 is required to elicit proper CNS angiogenesis ²⁷ . - TGFB1 expression increases in human brain tissue and cerebrospinal fluid after ischemia 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 ischemic stroke ³⁰ .
	RELN	Reelin		- Encodes a protein involved in migration of newborn neurons during development. Reelin deficiency impairs neurogenesis and exacerbates ischemic neuronal injury in the adult brain of mice ³¹ .

	RET	Ret proto-oncogene	<ul style="list-style-type: none"> - 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 ischemic stroke ³³.
	HBEGF	Heparin binding EGF like growth factor	<ul style="list-style-type: none"> - Encodes a member of the EGF family. It is induced by cerebral ischemia ³⁴ and contributes to functional recovery after ischemic stroke by promoting neurogenesis and angiogenesis ³⁵.
	ADM	Adrenomedullin	<ul style="list-style-type: none"> - Encodes a potent vasodilatory peptide which induces angiogenesis after ischemia 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 ischemia area of the brain ³⁸.
	ANGPT2	Angiopoietin 2	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 ischemic astrocytes in vitro. It inhibits both neurogenesis and oligodendrogenesis ⁴⁶.
		DLK1	Delta like non-canonical Notch ligand 1	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 ischemic stroke ⁴⁹.
		LGALS3	Galectin 3	<ul style="list-style-type: none"> - 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 ischemic stroke ⁵⁰.
		IL32	Interleukin 32	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Catalyzes the phosphorylation of sphingosine to form sphingosine-1-phosphate (S1P). SPHK and S1P activate signaling molecules implicated in the induction of cerebral ischemic tolerance ⁵². - SPHK1 is upregulated in the ischemic brain ⁵³.
		IL8RB (CXCR2)	C-X-C motif chemokine receptor 2	<ul style="list-style-type: none"> - 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 ischemic stroke ⁵⁴.

	IFNG	Interferon gamma	<ul style="list-style-type: none"> - 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 ischemic stroke which enhances neural injury ⁵⁵.
	PTX3	Pentraxin 3	<ul style="list-style-type: none"> - 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 ischemic brain injury. The absence of PTX3 strongly compromises blood-brain barrier integrity and resolution of brain edema during recovery after ischemic injury ⁵⁶.
	IL12A	Interleukin 12A	<ul style="list-style-type: none"> - 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 ischemic stroke ⁵⁵.
	IL1A	Interleukin 1 alpha	<ul style="list-style-type: none"> - 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 ischemia and leads to neuronal injury ⁵⁸.
	IL6	Interleukin 6	<ul style="list-style-type: none"> - Encodes a cytokine that functions in inflammation. After ischemic stroke, inflammatory cells can secrete cytokines such as IL6. IL6 is considered as a deteriorator of stroke outcome ⁵⁹.
	TNFRSF 14	TNF receptor superfamily member 14	<ul style="list-style-type: none"> - 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.
	TNFRSF 10D	TNF receptor superfamily member 10D	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 ischemia ⁶² .
		TNFRSF 12A	TNF receptor superfamily member 12A	- Encodes a member of the TNF receptor superfamily. Its expression is induced by brain ischemia/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. - Ischemic 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. - Ischemic 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. - Ischemia 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 ischemic brain injury ⁶⁸ . - ITGAM expression is up-regulated in response to ischemia 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. - Ischemic 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 ischemia 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.

				<ul style="list-style-type: none"> - Focal cerebral ischemia induces active proteases that degrade microvascular matrix proteins including laminin ⁷³.
		LAMA2	Laminin subunit alpha 2	<ul style="list-style-type: none"> - Laminins, a family of extracellular matrix glycoproteins, are the major noncollagenous constituent of basement membranes. - Focal cerebral ischemia induces active proteases that degrade microvascular matrix proteins including laminin ⁷³.
		COL4A1	Collagen type IV alpha 1 chain	<ul style="list-style-type: none"> - 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. - Ischemic stroke degrades extracellular matrix such as collagen and breaks down blood-brain-barrier ⁷⁰.
MMP		MMP12	Matrix metalloproteinase 12	<ul style="list-style-type: none"> - Encodes a member of the peptidase M10 family of matrix metalloproteinases (MMPs). MMPs are markers for the pathological ischemic 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 metalloproteinase 2	<ul style="list-style-type: none"> - Encodes a member of the peptidase M10 family of matrix metalloproteinases (MMPs). - Focal ischemia increases MMP2 activities in human brain ⁷⁸.
		TIMP1	TIMP metalloproteinase inhibitor 1	<ul style="list-style-type: none"> - 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 ischemia brain tissue at both 1 and 5 days after ischemia stroke in rat brain ⁷⁹.
Cell adhesion		SPARC	Secreted protein acidic and cysteine rich	<ul style="list-style-type: none"> - 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 ischemic

			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 ischemic 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 $\alpha 5$ 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	<ul style="list-style-type: none"> - 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 ischemic rat model ⁸⁷.
		NFLA	neurofilament, light polypeptide	<ul style="list-style-type: none"> - 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. - Ischemic 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)	<ul style="list-style-type: none"> - Encodes a protein that are enriched in the growth cones of neurites and involved in neurite extensions ⁹⁰.
		RTN4	Reticulon 4 (Nogo)	<ul style="list-style-type: none"> - Encodes a family of reticulon that inhibits neurite outgrowth ⁹¹. - RTN4 expression is upregulated in response to ischemia ⁹².
Synaptogenesis		GAP43	Growth associated protein 43	<ul style="list-style-type: none"> - 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 ischemia in the brain ⁹⁵.
		SIRPA	Signal regulatory protein alpha	<ul style="list-style-type: none"> - 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 ischemia ⁹⁷.
		PANX1	Pannexin 1	<ul style="list-style-type: none"> - 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 ischemia ¹⁰⁰.
		CDH2	Cadherin 2 (neuronal cadherin)	<ul style="list-style-type: none"> - 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 ischemia 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 ischemia. 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 syn1 is highly related to dentate neurogenesis and synaptogenesis after hippocampal injury caused by global ischemia 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 ischemia brain damage ¹⁰⁹ .
		NLGN3	Neuroigin 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 neuroigin 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 ischemia 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 .
		CAMK2 A	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	Glutamate	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 ischemic brain ^{116,117} .
		GRM1 (mGluR1)	Glutamate metabotropic receptor 1	- Encodes a G-protein coupled receptor for glutamate ¹¹⁸ . - Related to both neuroprotective and neurotoxic during ischemic 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

				aminobutyric acid (GABA), an inhibitory neurotransmitter ¹²⁶ .
		GABRB1	Gamma-aminobutyric acid type A receptor beta 1 subunit (GABA (A) receptor, beta 1)	<ul style="list-style-type: none"> - 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 ischemia in the brain ¹²⁸.
EC-EC junctions		CDH2	Cadherin 2	<ul style="list-style-type: none"> - 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. - Ischemic stroke disrupts BBB integrity ¹³⁰.
		CLDN3	Claudin 3	<ul style="list-style-type: none"> - Claudin proteins contributes to the physiological “seal” of the tight junction. Claudin-3 influences barrier function. - Ischemic 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	<ul style="list-style-type: none"> - 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. - Ischemic 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	<ul style="list-style-type: none"> - 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 ischemia 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.	<ul style="list-style-type: none"> - 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 ischemia 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. -Ischemic stroke disrupts BBB integrity and disruption of tight junction protein complexes is a hallmark of BBB disruption ¹³⁰ . - In a focal cerebral ischemia 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 ischemia-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 ischemia 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 ischemia/reperfusion injury ¹³⁸ .
Adhesion mol. for		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

				<p>endothelial cell-cell adhesion molecule that is involved in angiogenesis ¹³⁹.</p> <p>- PECAM-1 is a key participant in the adhesion cascade leading to extravasation of leukocytes during the inflammatory process like ischemic stroke ^{140,141}.</p>
		CXCR3	C-X-C motif chemokine receptor 3	<p>- 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.</p> <p>- 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.</p>
		ICAM1	Intercellular adhesion molecule 1	<p>- 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.</p> <p>- Ischemic stroke induces upregulation of ICAM-1. After focal brain ischemia, leukocytes adhere to the perturbed endothelium and are believed to aggravate reperfusion injury ¹⁴⁴.</p>
		CD44	CD44 molecule	<p>- 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.</p> <p>- Cerebral ischemia induces CD44 expression ¹⁴⁶.</p>
Pericyte markers	Reactive	CSPG4	Chondroitin sulfate proteoglycan 4 (NG2)	<p>- Known as a conventional pericyte marker ^{147,148}.</p> <p>- CSPG4 is upregulated in pericytes following chronic hypoxia ¹⁴⁹.</p>
		PDGFRB	Platelet derived growth factor receptor beta	<p>- Known as a conventional pericyte marker ^{147,148}.</p> <p>- Expression level of this gene in brain pericytes is gradually increased in the ischemic stroke model ¹⁵⁰.</p>
		ITGA5	Integrin subunit alpha 5 (CD49e)	<p>- Encodes a protein of integrin alpha chain family that associates with the beta 1 subunit to form a fibronectin receptor ¹⁵¹.</p>

				- 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 ischemic 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 ischemic 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 ischemic 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.

				<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 ischemia 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))	<ul style="list-style-type: none"> - Encodes a chemokine of the CXC subfamily and ligand for the receptor CXCR3 ¹⁷⁰. - Expression level of CXCL10 is higher in ischemic stroke patients than in healthy controls ¹⁷¹. 	
		VIM	vimentin	<ul style="list-style-type: none"> - 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)	<ul style="list-style-type: none"> - 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 ischemia in the brain ¹⁷⁴. 	
	A1		C3	complement C3	<ul style="list-style-type: none"> - 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 (ischemia) reactive astrocytes ¹⁷⁶.
			C1R	complement C1r	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Encodes a transmembrane 4 superfamily with four hydrophobic domains ¹⁸¹. - Markers of A2 reactive astrocytes ¹⁸².
AC-neuron interaction		NLGN3	Neuroigin 3	<ul style="list-style-type: none"> - Encodes a member of neuronal cell surface proteins family. Neuroligin proteins expressed by cortical astrocytes, control astrocyte morphogenesis through interactions with neuronal neuexins ¹⁸³.
		FABP7	Fatty acid binding protein 7	<ul style="list-style-type: none"> - 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 ischemia in young adult monkeys ¹⁸⁵.
		S100A6	S100 calcium binding protein A6	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - S100B, synthesized in considerable amounts in astrocytes, modulates long-term synaptic plasticity ¹⁸⁷. - Ischemic 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	<ul style="list-style-type: none"> - Lipopolysaccharide (LPS) treatment can induced IFITM3 expression in astrocyte ¹⁸⁹. - Astrocyte expressing IFITM3 mediates long-lasting neuronal impairments ¹⁹⁰.
Microglia reactive markers	Pan	CD68	CD68 molecule	<ul style="list-style-type: none"> - CD68 is a lysosomal membrane marker and stains microglia in a highly active, phagocytising state ¹⁹¹. - Stroke is a powerful stimulus that triggers microglia activation ¹⁹².

		IBA-1	(Allograft inflammatory factor 1) Ionized calcium-binding adapter molecule 1	<ul style="list-style-type: none"> - 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 ischemia ¹⁹³.
	M1	CD86	CD86 molecule	<ul style="list-style-type: none"> - Microglia activated by ischemic stroke exhibit a spectrum of phenotypes, release both pro- (M1 microglia) and anti-inflammatory (M2 microglia) mediators, and function to either exacerbate ischemic 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. - Ischemic stroke increased the expression of CD86 ¹⁹⁴.
		BIRC3	Baculoviral IAP repeat containing 3	<ul style="list-style-type: none"> - 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 ischemic stroke ¹⁹⁶.
		CD40	CD40 molecule	<ul style="list-style-type: none"> - 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 ischemia ¹⁹⁷.
	M2a	CD206 (MRC1)	mannose receptor C-type 1	<ul style="list-style-type: none"> - 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 ischemic core to promote tissue repair ²⁰⁰.
		CD200R 1	CD200 receptor 1	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 ischemic 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 ischemic 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 ischemic 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 ischemic 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 (CXCL3) 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 ischemic stroke ¹⁹⁸ . The expression of CXCL9 is

				elevated 24 h after ischemia-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 immunoregulatory and inflammatory processes. - CXCL2 expression is induced in ischemic 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 ischemic 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 ischemic 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 ischemia ²⁰² . - TLR2 is upregulated after focal cerebral ischemia 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 ischemia ²⁰⁴ .
		TLR3	Toll like receptor 3	-TLR3 is not found to have association with outcome or infarct volumes in ischemic stroke patients ²⁰⁵ .
		TLR4	Toll like receptor 4	- Participates in the inflammatory reaction. Its expression increases after focal ischemia 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 ischemic 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 ischemic 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 . - Ischemic 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 ischemic 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 ischemia. 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.

				- Ischemic 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 ischemic 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 ischemic 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 ischemic 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 ischemic 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 ischemic 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 ischemic 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 ischemic 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 ischemia 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 ischemia 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 ischemia ²³⁰ .
	AHR	Aryl hydrocarbon receptor		- Encodes a transcriptional regulator involved in adaptive xenobiotic response and immune response ²³¹ . - AHR expression is increased in ischemic 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 ischemic 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. <i>Irf8</i> ^{-/-} 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 ischemia 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 .

Table S3. 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 ischemia-reperfusion injury in mice ²⁴² . - ADORA1 negatively regulates adult neurogenesis while promoting astroglialogenesis 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 recruit 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 .

		<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 ischemic 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Regulates cell proliferation and differentiation ²⁹³ and stimulates neurogenesis ²⁹⁴.

EP300	E1A binding protein p300	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Colocalizes in the membrane rafts with GM3, a ganglioside that serves regulatory roles in axonogenesis ²⁹⁷.
FGF2	Fibroblast growth factor 2	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Acts as neurotrophic factor promoting neuron growth.
GRIN1	Glutamate ionotropic receptor NMDA type subunit 1	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Suppresses cell-cycle progression ³⁰⁹. Cell proliferation was suppressed by knockout of HDAC4 ³¹⁰. - In responses to cerebral ischemia, HDAC4 serves as an important HIF-VEGF signal-sensitive molecule to modulate angiogenesis, which promotes neurogenesis ³¹¹.
HES1	Hes family bHLH transcription factor 1	<ul style="list-style-type: none"> - Encodes a protein that belongs to the basic helix-loop-helix family of transcription factors. Expression of this gene is induced by the Notch

		<p>signaling pathway that inhibits neuronal and muscle differentiation ³¹².</p> <p>- Expression of this gene is induced by the Notch signaling pathway. Level of Hes1 increased after ischemia and decreased during the differentiation of neural progenitor cells ³¹³.</p>
HEY1	Hes related family bHLH transcription factor with YRPW motif 1	<p>- Expression of this gene is induced by the Notch signaling pathway ³¹³.</p> <p>- Promotes maintenance of neural precursor cells ³¹⁴.</p>
HEY2	Hes related family bHLH transcription factor with YRPW motif 2	<p>- Expression of this gene is induced by the Notch signaling pathway ³¹³.</p> <p>- Promotes maintenance of neural precursor cells ³¹⁴.</p>
HEYL	Hes related family bHLH transcription factor with YRPW motif-like	<p>- Expression of this gene is induced by the Notch signaling pathway ³¹³.</p> <p>- Promotes neuronal differentiation of neural progenitor cells both in culture and in the embryonic brain in vivo ³¹⁵.</p>
IL10	Interleukin 10	<p>- IL10 is a key immune regulator and acts as an anti-inflammatory cytokine.</p> <p>- Patients have significantly lowered IL-10 serum levels soon after the acute event, with a slight increase at the seventh day ²³⁷.</p>
IL3	Interleukin 3	<p>- Promotes cell growth ³¹⁶ and possessed neurotrophic activity ³¹⁷.</p> <p>- 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.</p>
KMT2A (Mll1)	Lysine methyltransferase 2A	<p>- Encodes a transcriptional coactivator that plays an essential role in neurogenesis by regulating neural progenitor proliferation and neuronal and glial differentiation ³¹⁹.</p>
LIF	LIF interleukin 6 family cytokine	<p>- 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.</p> <p>- Promotes neurogenesis ³²⁰, affects neuronal differentiation, and peripheral nerve regeneration ³²¹.</p>
MAP2	Microtubule associated protein 2	<p>- Mainly expressed in neurons and involves in axonogenesis in developing cortical and hippocampal neuronal cultures ³²².</p>
MDK	Midkine	<p>- 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.</p> <p>- Promotes a variety of cellular functions leading to increased angiogenesis, proliferation, migration, and survival ³²⁶.</p>

		- 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 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 ischemia. 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 ischemic brain ³⁴⁸ .

P2RY1	Purinergic receptor P2Y1	<ul style="list-style-type: none"> - 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 ischemia ³⁵⁰.
P2RY2	Purinergic receptor P2Y2	<ul style="list-style-type: none"> - 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 ischemic stroke in the Han Chinese population ³⁵².
PAFAH1B1	Platelet activating factor acetylhydrolase 1b regulatory subunit 1	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 astroglialogenesis 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	<ul style="list-style-type: none"> - Encoded a protein that is involved in the conversion of tyrosine to dopamine. - Promotes dopaminergic neurogenesis ³⁸⁶.
TNF	Tumor necrosis factor	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Protects cells from apoptosis ³²³ and promotes neurogenesis, neuronal migration, neuronal survival and axon guidance ³²⁴. - Guides angiogenesis ³⁴⁴.

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