Notch signaling in cerebrovascular diseases (Review)

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Abstract. The Notch signaling pathway is a crucial regulator of numerous fundamental cellular processes. Increasing evidence suggests that Notch signaling is involved in inflammation and oxidative stress, and thus in the progress of cerebrovascular diseases. In addition, Notch signaling in cerebrovascular diseases is associated with apoptosis, angiogenesis and the function of blood-brain barrier. Despite the contradictory results obtained to date as to whether Notch signaling is harmful or beneficial, the regulation of Notch signaling may provide a novel strategy for the treatment of cerebrovascular diseases.

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1. Introduction

Cerebrovascular diseases occur following acute cerebrovascular events whereby the arteries of the brain are blocked or a brain blood vessel ruptures. Poor blood flow to the brain subsequently results in cell death. There are three primary types of cerebrovascular diseases: Ischemic stroke, hemorrhagic stroke and transient ischemic attack (TIA). The high incidence of cerebrovascular diseases worldwide is largely due to failed management and prevention of modifiable risk factors, particularly in ischemic stroke, which accounts for >85% of total cerebrovascular diseases. Cerebrovascular diseases more commonly affect people who are overweight, aged ≥55, have a unhealthy lifestyle (limited exercise, heavy drinking, use of illicit drugs, smoking or poor work/life balance), and who have a family history of stroke, hypertension, moyamoya, vasculitis, arterial dissection or venous occlusive disease (1-6). Cerebrovascular disease is the leading cause of mortality and chronic disability in China, and the third leading cause of mortality and the leading cause of chronic disability in the USA (7,8).

Notch signaling is a major intercellular communication pathway, which is highly conserved in the majority of multicellular organisms. Notch signaling is a crucial regulator of numerous fundamental cellular processes, including proliferation, stem cell maintenance and differentiation, during embryonic development in vertebrate and invertebrate organisms (9-11). In addition, Notch signaling is involved in cell differentiation, proliferation, inflammation (12), oxidative stress and apoptosis in a variety of cell types in adults (10,13). The primary mechanisms underlying the Notch signaling pathway in cerebrovascular disease have been well-established by extensive investigation (10,14,15), and include enhancing inflammation (16-18), increasing oxidative stress (19), promoting apoptosis (20) and mediating adult subventricular zone neural progenitor cell proliferation and differentiation following stroke (21). It has been demonstrated that activation of the Notch signaling pathway exacerbates ischemic brain damage, whereas inhibiting the Notch signaling pathway decreases the infarct size and improves the functional outcome in a mouse model of stroke (18,22).

The present review discusses the role of the Notch signaling pathway in the pathogenesis of cerebrovascular diseases. It primarily focuses on the association between Notch signaling and neuroinflammation, oxidative stress and apoptosis in cerebrovascular diseases. An overview is provided for the proposed pathogenic mechanism underlying Notch signaling

in stroke via regulation of angiogenesis and the function of the blood-brain barrier (BBB). Finally, the efficacy of regulating Notch signaling as a novel therapeutic intervention for cerebrovascular diseases is considered.

2. Notch signaling pathway

The Notch gene, discovered in the wings of *Drosophila melanogaster* by Thomas Hunt Morgan in 1917 (23), is crucial for the regulation of various physiological processes (24,25). The Notch signaling pathway, comprised of Notch receptors (Notch1, Notch2, Notch3 and Notch4), Notch ligand and the transcription factor, CBF1/Suppressor of Hairless/LAG-1 (CSL) protein, is critical for numerous fundamental cellular processes, including proliferation, differentiation and survival, during embryonic and adult development (26-30). These effects are mediated by the transmembrane ligand-induced release of the Notch intracellular domain (NICD) and the interaction of this fragment with the CSL family of transcription factors within the nucleus (25,27,31). The Notch receptors are expressed on cell membrane surfaces, and thus can be cleaved by a disintegrin and metalloproteinase (ADAM) 17 or -10 and a presenilin-dependent γ-secretase complex. The cleaved NICD translocates to the nucleus, where it interacts with the ubiquitous transcription factor CSL and recruits co-activator mastermind-like proteins and therefore activates downstream target genes (32-34). In addition, CSL may inhibit the expression of target genes by forming transcription complexes in the absence of NICD.

Extensive evidence has revealed that the Notch signaling pathway is closely associated with the function and structure of the nervous system. In the central nervous system (CNS), the Notch signaling pathway regulates the normal development of neural progenitor cells, neurons, oligodendrocytes and astrocytes (35,36). Numerous diseases of the nervous system are associated with Notch mutations, including sporadic Alzheimer's disease (37,38), Down syndrome (39,40), Pick's disease (38) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (41-44). The molecular and cellular mechanisms underlying the degeneration of brain cells affected by cerebrovascular disease are complex, involving bioenergetic failure, acidosis, excitotoxicity, oxidative stress and inflammation, and resulting in necrotic or apoptotic cell death (45,46). Various signaling pathways are involved, including Notch. For example, in cerebral ischemia, the activation of Notch regulates nerve damage repair, inflammation and angiogenesis in the vascular ischemic area via regulating proliferation and development of neuronal precursor cells, mediating the release of inflammatory factors and promoting angiogenesis (47-50). Studies *in vitro* and *in vivo* have demonstrated that blood vessel angiogenesis, endothelial cell proliferation, and artery and vein differentiation are regulated by the Notch signaling pathway (51-53). Enhancing Notch signaling activity promotes arteriogenesis via vascular smooth muscle cell (VSMC) proliferation in the ischemic brain following stroke (51,54,55).

3. Notch signaling and neuroinflammation in cerebrovascular diseases

Inflammation is a complex cascade that protects the body from infection and injury. Similarly, neuroinflammation is a response to neurological damage and may be divided into acute and chronic process. A variety of inflammatory cytokines take part in the neuroinflammation. Evidence indicates that acute neuroinflammation is beneficial to damage repair in the nervous system, whereas chronic neuroinflammation aggravates the pathological events occurring in the brain (56-59). In addition, neuroinflammation has been demonstrated to be crucial for the pathogenesis of cerebrovascular diseases (56). Various studies have revealed that the activation of Notch signaling promotes the neuroinflammatory response associated with cerebrovascular diseases (Fig. 1) (18,22,60).

Notch signaling and cytokines. Previous studies have demonstrated that cerebral ischemia initiates an inflammatory response in the brain associated with the release of a variety of inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 (55,61,62). Macrophages treated with Toll-like receptor (TLR) 3 or -4 agonists increase their production of interferon (IFN)-β, TNF-α, IL-12 and IL-23. Activation of glial cells and their release of neurotoxic factors enhance inflammation in cerebrovascular disease. In addition, activated glial cells increase the expression of inflammatory cytokines in cerebral ischemia, including TNF-α, IL-1β, IL-6, transforming growth factor β (TGF-β) and IL-8.

Notch signaling is evolutionarily conserved and critical for the development and homeostasis of various tissues. Activation of Notch signaling promotes macrophage polarization to the IFN-γ-producing M1 (inflammatory) subtype (63). Inhibition of Notch signaling by γ-secretase inhibitors (GSI) reduces nuclear factor-κB (NF-κB) activity and suppresses inflammatory responses. Previous studies have demonstrated that GSI significantly decreases peptidoglycan and poly (I:C)-induced secretion of M1 (TNF-α, IL-6, IFN-γ and IL-1α) and the anti-inflammatory subtype M2 (IL-10) cytokines (63,64). Notch signaling is activated in response to TLR ligands, thus amplifying the inflammatory response by enhancing NF-κB signaling. Activation of Notch signaling has been revealed to be involved in the sustained activation of NF-κB and the resulting enhancement of inflammatory responses (65). It is becoming apparent that Notch signaling is central to chronic inflammatory events involved in the pathogenesis of cerebrovascular diseases, and Notch may therefore provide a novel target for therapeutic strategies (15,16,18-20,22,63,65). An ischemic stroke rat model induced by a 90-min occlusion of the right middle cerebral artery demonstrated that inhibiting Notch activation with N-[N-(3,5-Difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester (DAPT) limited NICD release, and production of IL-6 and IL-1β in the ischemic penumbral cortex (18). Notch mutations may result in a predisposition to stroke and cerebrovascular atherosclerosis, and Notch mutations may also be involved in inflammation process, as genes encoded by Notch mutations include the IL-1 receptor and paraoxonase-1 (66).

Notch signaling and inflammatory mediators. Inflammatory mediators from plasma or cells, exert their effects via binding to specific receptors on target cells. Mediators may have one or numerous target cell types, and may even have varying effects in distinct cell and tissue types. It has been demonstrated that Notch signaling may reprogram mitochondrial metabolism for proinflammatory macrophage activation, inducing the release

Table I. Potential role of Notch signaling in stroke via inflammatory mediators.

Mediator	Source	Potential role in stroke	References
Histamine and serotonin	Mast cells, platelets	Enhancing vascular leakage, regulating cell proliferation and differentiation	74-76
Bradykinin	Plasma substrate	Enhancing vascular leakage and pain	77
C3a	Plasma protein via liver	Enhancing vascular leakage and the formation of opsonic fragment (C3b)	78
C5a	Macrophages	Enhancing vascular leakage, chemotaxis and leukocyte adhesion and activation	79
Prostaglandins	Mast cells from membrane phospholipids	Potentiating other mediators, vasodilation, pain and fever	80,81
Leukotriene B4	Leukocytes	Leukocyte adhesion and activation	82
Oxygen metabolites	Leukocytes	Endothelial damage and tissue damage	22,83-85
IL-1 and TNF-α	Macrophages, other	Acute phase reactions, enhancing vascular leakage and endothelial and tissue damage	18,65,68, 86-89
Chemokines	Leukocytes, others	Leukocyte activation, enhancing vascular leakage and endothelial and tissue damage	90-92
Nitric oxide	Macrophages, endothelium	Vasodilation and cytotoxicity	71

C, complement component; IL-1, interleukin-1; TNF-α, tumor necrosis factor α.

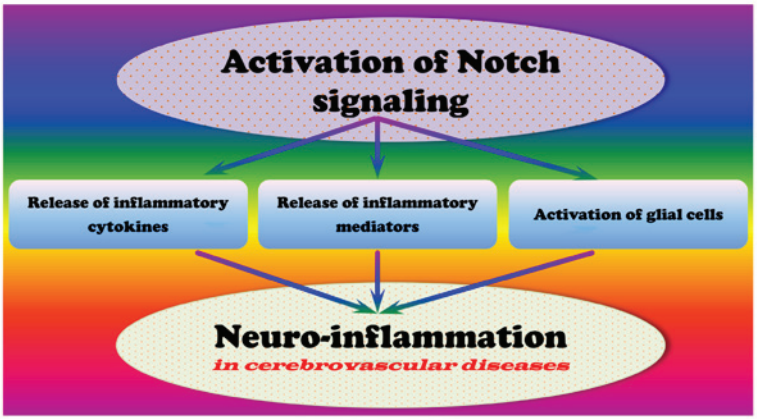

Figure 1. Potential underlying mechanisms by which the activation of Notch signaling may contribute to the pathogenesis of neuroinflammation in cerebrovascular diseases.

of inflammatory mediators (67). Nitric oxide (NO), which is produced by cells that express NO synthase (NOS), is a prevalent inflammatory mediator that may inhibit the activity of Notch1 signaling (68,69). A previous study indicates that inducible NOS (iNOS) is directly involved in the generation of NO and the inhibition of Notch1 signaling, and that NO inhibits the binding of Notch1-IC and CSL protein transcriptional complexes to a specific target sequence (69). The dysfunction of Notch signaling pathway increases the vulnerability of neurons and interacts with NF-κB to enhance the inflammatory response following cerebral ischemia (70,71). Numerous signaling pathways involved in neurodegenerative disorders are activated in response to reactive oxygen species (ROS), which induce apoptosis and increase NICD release and the expression of hairy and enhancer of split-1 (HES-1) in cerebral ischemia (71-73). The potential role of Notch signaling in stroke via inflammatory mediators is summarized in Table I.

Notch signaling and glial cells (microglia and astrocytes). Microglia are mononuclear phagocytes with various functions in the CNS, with the stage and function of microglia indicated by morphological characteristics. The phagocytic function of microglia is critical for the removal of hematoma and other debris; however, they additionally produce inflammatory mediators (93). Microglia are typically classified into three forms: Ameboid, ramified and activated. Microglia, as the resident immune cells of the CNS, continually sample the environment. Under normal conditions, they exist in a ramified form and phagocytose debris (94). Previous studies indicate that Notch signaling may regulate the different forms of microglia under different conditions (71,95-97). Notch signaling damages neurons by activating microglial cells and stimulating the infiltration of proinflammatory leukocytes (98). Following stroke, microglia are activated, become amoeboid and release inflammatory cytokines (M1 subtype). However,

microglia may be differentially activated, subsequently limiting inflammation and destroy tissue debris through phagocytosis (M2 subtype) (63,99). Microglia secrete various inflammatory molecules, including IL-1, IL-6, IFN-γ and TNF-α (22). Furthermore, Notch signaling may be involved in regulating microglia activation following hypoxia, partially via the TLR4/Myeloid differentiation primary response gene 88/TNF receptor associated factor 6/NF-κB signaling pathway (71,100). A model of focal ischemic stroke using mice transgenic for antisense Notch or wild-type mice treated with GSI demonstrated that inhibiting Notch activation reduced brain cell damage and improved functional outcome. This suggests that Notch activation exacerbates brain damage and functional outcome in ischemic stroke (98). Therefore, Notch signaling may be a potential target for inhibition of microglia activation implicated in brain damage (101).

Notch signaling and neuroinflammation in cerebrovascular diseases. Various studies have indicated that Notch activation induces NF-κB-mediated expression of proinflammatory genes in hypoxic astrocytes (102). Notch signaling regulates the activation state of microglia, thus contributing to the control of inflammatory reactions in the CNS (18,96). Notch-1 signaling is activated in hypoxic astrocytes, verified by increased NICD and HES-1, regulating astrocytic proliferation and activation via the suppression of the vascular endothelial growth factor (VEGF) or NF-κB signaling pathways. Dysregulation of Notch may exert effects following stroke via the activation of microglia and astrocytes (63,72,87,103). NF-κB is crucial in promoting ischemic brain damage following stroke. Activation of NF-κB induces the expression of proinflammatory cytokines, the adhesion and migration of leukocytes, thus increasing the inflammatory response (102). The Notch1 signaling pathway regulates the NF-κB signaling pathway via Jagged1 and inhibitor of κB α (IκBα). The dysfunction of the Notch signaling pathway occurs with NF-κB following cerebral ischemia via activating microglia to produce inflammatory mediators (71,101,104). In addition, Notch activation enhances postischemic inflammation by directly modulating the microglial innate response (22,104). In rats with cerebral ischemia and in activated BV-2 microglia, Notch signaling induces the migration and morphological transformation of activated microglia (16). An ischemic rat model using middle-cerebral-artery occlusion demonstrated that Notch-Jagged signaling is involved in dysfunction of astrocyte-associated capillary network (103).

4. Notch signaling and oxidative stress in cerebrovascular diseases

Oxidative stress is broadly defined as a disturbance in the balance between ROS production and antioxidant defenses (105-107). In this state, abnormal levels of ROS, including free radicals (hydroxyl, nitric acid and superoxide) and non-radicals (hydrogen peroxide and lipid peroxide) result in oxidative damage to cells or tissue (105,108-111). The oxidation state is the sum of all redox processes producing ROS, reactive nitrogen species and other reactive intermediates (106,108,112-114). ROS are crucial for physiological processes, including apoptosis, regulation of neurotransmitters and chemotaxis (114-116). ROS may destroy cell function and promote injury to cellular lipids, nucleic acids and proteins, thus inducing apoptosis. Oxidative stress is associated with the pathological process of atherosclerosis, diabetes, neurodegenerative disorders including Alzheimer's disease and Parkinson's disease (117,118), hypertension (119,120), cardiovascular diseases (121) and cerebrovascular diseases (122,123). These diseases may promote the production of ROS (105,107).

Oxidative stress and cerebrovascular diseases. Oxidative stress is involved in the pathogenesis of ischemic and hemorrhagic stroke (124-130) and appears to be a typical feature in diverse models of cerebrovascular disease. Additionally, oxidative stress may be involved in the pathogenesis of acute ischemic stroke (131-136). Oxidative stress regulates cerebral blood flow and controls permeability of the BBB (115,137). A high quantities of superoxide, NO and peroxides are generated during cerebral ischemia/reperfusion, and cellular macromolecules are destroyed by oxygen radicals, resulting in apoptosis (138-142). Oxygen radicals activate matrix metalloproteinases, resulting in the degradation of collagen and laminin proteins in the basilar membrane, and destroying the integrity of the vessel wall (143). In addition, ROS may induce cell death through oxidative modification and fragmentation of DNA mediated by nucleate endonuclease (144-146). Furthermore, oxidative stress promotes transmigration of neutrophilic granulocytes from peripheral blood to the CNS and the release of enzymes that degrade the blood vessel basement membrane, resulting in increased permeability of blood vessels (147-149). Oxidative stress may result in the dysregulation of endothelial cell function, caused by hyperglycemia, dyslipidemia and hyperinsulinemia, leading to impaired vasoregulation, inflammation and altered BBB function (150-152). The described pathological processes result in cerebral parenchymal hemorrhage, vasogenic brain edema and neutrophil infiltration, thus, aggravating cerebral ischemic injury (142,153,154).

Notch signaling and oxidative stress in cerebrovascular diseases. Studies have revealed that oxidative stress may activate multiple signaling pathways associated with cell death; the Notch signaling pathway is closely associated with oxidative stress following cerebral ischemia, suggesting that dysregulation of Notch signaling contributes to the occurrence of oxidative stress (Fig. 2) (155-158). Notch activation results in cell proliferation and metastasis, accompanied by a decrease in B-cell lymphoma-2 (Bcl-2) associated protein X (Bax), Bcl-2 antagonist/killer, cytochrome c and caspase-3 and p53 expression and an increase in Bcl-2 expression (159). It has been reported that inhibiting Notch signaling abrogated cerebral ischemia/reperfusion injury via inhibiting oxidative stress (68,160,161). Inhibiting the Notch signaling pathway attenuates endothelial oxidative stress injury (158), suggesting that Notch inhibition protects against cerebrovascular diseases via decreasing oxidative stress-induced endothelial injury (158). A mutation in Notch3 has been associated with mitochondrial disease, in which oxidative stress caused by chronic hypoxia results in cerebral arteriopathy (162).

Ischemia/reperfusion injury increases the oxidative stress levels in tissue. The role of the Notch signaling pathway in the

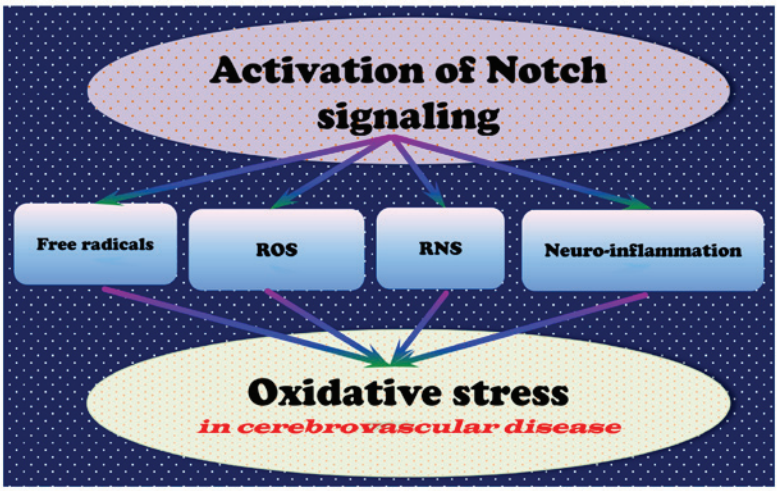

Figure 2. Potential underlying mechanisms by which activation of Notch signaling may contribute to the pathogenesis of oxidative stress in cerebrovascular diseases. ROS, reactive oxygen species; RNS, reactive nitrogen species.

oxidative stress-associated pathogenesis of cerebrovascular diseases has been researched extensively (163). Further investigations to elucidate the underlying molecular mechanisms of the Notch signaling pathway in cerebrovascular disease may uncover potential drug targets for the treatment of Notch-associated diseases. However, decreasing the activity of Notch1 increases the production of superoxide anion, iNOS, NO, nitrotyrosine and phosphatase and tensin homolog deleted on chromosome 10 in mice subjected to ischemia/reperfusion injury, whereas the phosphorylation levels of NOS and protein kinase B (Akt) are decreased (68,163,164). As the inhibition or activation of Notch signaling may be beneficial for the treatment of cerebrovascular diseases, Notch signaling may exert distinct functions under different conditions. Therefore, further studies are required to elucidate the mechanisms underlying the role of Notch signaling in cerebrovascular diseases.

5. Notch signaling and apoptosis in cerebrovascular diseases

Programmed cell death by apoptosis is crucial for the development of multicellular organisms, and defects in apoptosis are associated with a wide variety of diseases (165). Inappropriate apoptosis results in tissue atrophy, whereas a failure of apoptosis, as occurs in cancer, leads to uncontrolled cell proliferation. Certain factors, including Fas receptors and caspases, induce apoptosis, whereas others, including certain Bcl-2 family members, suppress it (166). Apoptosis is induced by either the extrinsic or intrinsic pathways (167,168). Extrinsic stimuli include the binding of ligands to cell surface death receptors, hormones, TNF-α, growth factors, NO and cytokines (169-171). Intrinsic signals result from cellular stress, including heat, radiation, nutrient deprivation and viral infection. The expression of pro- and anti-apoptotic proteins, the strength of the stimulus and the cell cycle stage all alter the response of the cell to the extrinsic or intrinsic trigger (172,173).

Apoptosis and cerebrovascular diseases. In vivo and *in vitro* studies suggest that apoptosis is critical for the pathogenesis of cerebrovascular diseases (174-179). Increased expression of apoptotic proteins, including phosphorylated (p)-Arabidopsis serine/threonine kinase 1 (ASK1), p-c-Jun N-terminal kinase (JNK), p-p38, cleaved caspase-3 and cytochrome c in the ischemic penumbra has been observed following stroke (177). Studies have reported that the inhibition of apoptosis may prevent the development of cerebral ischemia/reperfusion injury (166,180-185). Thioredoxin-1 (Trx1) small interfering RNA increases ASK1 activation in response to apoptotic stress, Trx1 may therefore be anti-apoptotic and suppress cerebral ischemia/reperfusion injury (186-188), potentially via inhibition of the ASK1-JNK/p38 signaling pathway.

Notch signaling and apoptosis. Notch is involved in various physiological processes, via NICD translocation into the nucleus and binding to target genes (189-191), including apoptosis (172). During apoptosis of tumor cells, microRNA (miR)-100 was demonstrated to mediate Notch signaling (192). A previous study demonstrated that a Notch cis-regulatory element is responsive to loss and gain of Drosophila p53 (Dp53) function and that overexpression of Dp53 upregulates Notch mRNA and protein expression levels (165). Dp53-induced Notch activation and proliferation was revealed to occur even when apoptosis was inhibited, and Dp53 may have a dual role in regulating cell death and proliferation gene networks, to control the balance between apoptosis and proliferation (165). In addition, Notch may be important in the apoptosis- and drug-resistance of chronic lymphocytic leukemia cells. Notch signaling has a cardioprotective effect by regulating apoptosis via inhibiting Bcl-2 and the activation of caspase-3 and -9. Furthermore, the Notch signaling pathway mediates high-glucose-induced podocyte apoptosis via the Bcl-2 and p53 pathways (193-195). It has been reported that miR-34c overexpression increases the expression of anti-apoptotic Bcl-2, and decreases the expression of pro-apoptotic Bax and cleaved caspase-3 via targeting of Notch1 and Jaggged1 (193).

Notch signaling and apoptosis in cerebrovascular diseases. The Notch signaling pathway leads to apoptosis of nerve cells and glia. Cell death in the brain following stroke is the result of an alteration in the balance between pro- and anti-apoptotic

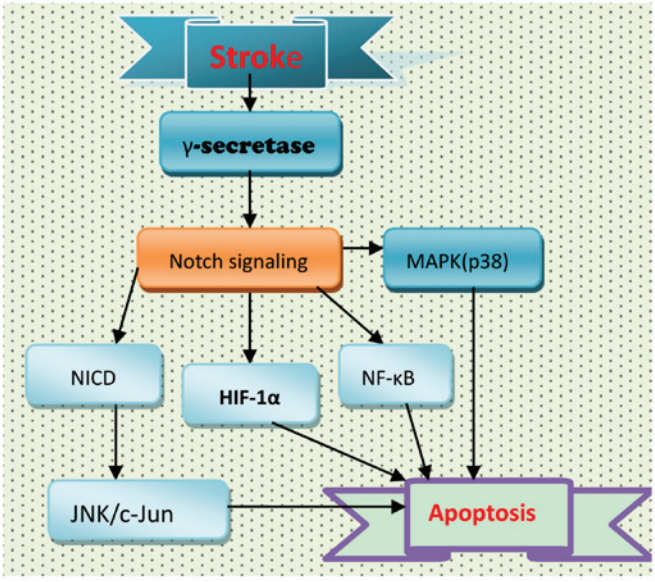

Figure 3. Potential association between apoptosis and Notch signaling following stroke. MAPK, mitogen-activated protein kinase; NICD, Notch intracellular domain; HIF-1α, hypoxia inducible factor-1α; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor-κB.

factors (196). Neurons undergo apoptosis and necrosis. The Notch signaling pathway is activated by various brain insults, including cerebrovascular diseases (20,47,197), and is associated with the apoptosis involved in the pathogenesis of stroke (Fig. 3). Following stroke, activation of the Notch signaling pathway may result in apoptosis of neurons via NF-κB and hypoxia inducible factor-1α (HIF-1α) (20,197,198). In addition, Notch signaling may affect mitogen-activated protein kinase (MAPK)-associated signaling pathways. However, the role of Notch signaling in MAPK activation following stroke remains to be fully elucidated. In wild-type and NICD1-overexpressing HEK and SH-SY5Y cell lines, ischemic conditions increased the expression levels of NICD1, JNK, p38-MAPK and cleaved caspase-3; this increase in NICD1 and JNK was attenuated by GSI (198). NICD overexpression increased JNK expression levels, resulting in enhanced cell death. Therefore, the Notch signaling pathway may contribute to ischemic stroke via the JNK signaling pathway (198), and the use of GSIs may be a potential strategy for the treatment of ischemic stroke.

Neuronal cell apoptosis associated with Notch signaling occurs in ischemic penumbra and ischemia/reperfusion injury following ischemic cerebrovascular disease (85,199-201). Notch signaling may contribute to apoptosis via the NF-κB, Bcl-like protein 11 and caspase pathways (202). Calsenilin, the expression of which is increased in the brain following experimental ischemic stroke, was revealed to enhance the γ-secretase-mediated cleavage of Notch and to contribute to apoptosis (203). Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) contributes to the pathogenesis of ischemic stroke by promoting Notch signaling *in vitro* and in a mouse stroke model, suggesting that Notch signaling activation is involved in the pathogenesis of stroke, and that inhibition of Pin1 may be a novel strategy for the treatment of ischemic stroke (204). However, Notch1 may inhibit neuronal apoptosis in cerebral ischemia/reperfusion injury via increasing the phosphorylation of Akt and promoting inactivation of Bcl-2-associated death promoter. Notch1 may be neuroprotective in the immature brain against ischemic injury, and future studies and clinical trials are required to investigate the suitability of Notch1 inhibitors as a treatment for perinatal ischemia. Inhibiting Notch2 was demonstrated to alter the levels of apoptosis-regulating proteins and slow the process of apoptosis in cerebral ischemia/reperfusion-induced mice (199). Loss-of-function mutations in Notch3 have been identified as the underlying cause of CADASIL (205,206), in addition to complex regulation of multiple pathways, including the Wnt/β-catenin signaling pathway, TGF-β and Notch-induced apoptosis (207).

In summary, the role of Notch signaling in stroke remains controversial. The majority of studies suggest that Notch signaling activation is damaging following stroke, promoting inflammation and apoptosis (20,83,98,202,206,208). However, certain studies have indicated that enhancing Notch signaling may improve stroke pathology (209-211). The effect of Notch on apoptosis is summarized in Table II. Therefore, further studies are required to fully elucidate the role of Notch signaling in stroke.

6. Notch signaling and angiogenesis in cerebrovascular diseases

Angiogenesis is a pathophysiological process of vessel branching to form a new capillary network via vascular endothelial cell proliferation and migration, and the sprouting and division of blood vessels (233-236). The vasculature is primarily comprised of vascular endothelial cells, VSMCs and extracellular matrix, the structure and activity of which affect the morphology and function of blood vessels. Angiogenesis is the result of the interaction between endothelial cells, stromal cells and cytokines mediated by a variety of positive and negative angiogenic modulators. Studies have revealed that VEGF/VEGF receptor (VEGFR) (237), Delta-like ligand 4 (DLL4)/Notch are the two primary pathways involved in the promotion and coordination of angiogenesis (Fig. 4) (238,239).

Lumen formation is required to establish mature blood vessels with complete structure and function. Vascular endothelial cells are divided into acute (tip cell) and lotus cells (trunk cell) depending on their location and characteristics, and are involved in the formation of lumen. High concentrations of VEGF-A induce endothelial cells to differentiate into tip cells. Tip cells extend filopodia through the extracellular matrix, along the VEGF-A gradient, providing direction to the new blood vessel branch. The proliferation of trunk cells behind the tip cell induces vascular sprouting, and the formation of the lumen and extended vascular network. High levels of VEGF induce the synthesis of DLL4 by tip cells, and thus increase Notchl expression in the adjacent trunk cells. The activation of the DLL4/Notchl signaling pathway promotes lumen formation (240,241). DLL4 expression in mouse tip cells was reduced and angiogenesis attenuated following treatment with VEGF antagonists or gene silencing (242,243). Studies have indicated that DLL4/Notch regulate tip and trunk cell number and differentiation, to control blood vessels sprouting and branching. Vascular sprouting and branching proceeds

Table II. Associations between apoptosis biomarkers and Notch signaling.

Apoptosis biomarker	Notch	Effect on apoptosis	References
p53	Notch (↑)	Inhibiting	195,212,213
Bcl-2	Notch1, Notch2 (↓)	Anti-apoptosis	195,202,214
Bax (↑)	Notch 1 (↑)	Apoptosis (↑)	215
Caspase-9 and -3 (↑)	Notch (↓)	Initiating	216,217
JNK/p38	Notch (↑)	Apoptosis (↑)	198,218
Ca^{2+} (↑)	Notch 2 (↑)	Apoptosis (↑)	219,220
ERK	Notch (↑)	Apoptosis (↑)	221
miR-100 (HS3ST2↑)	Notch (↑)	Initiating	192,222
NF-κB	NICD (↑)	Apoptosis (↑)	188
EGFR	Notch-1	Positive correlation	223,224
Jagged2, angiopoietin 1, eNOS (↓)	Notch2, Notch4, Notch3 (jagged1)	Caspase 8 (↑)	225
P21/cyclin D	Notch 2 (↑)	Apoptosis (↑)	226
PI3K/Akt (↑)	Notch (↓)	Podocyte apoptosis (↓)	193,194,226,227
ROS	Notch (↑)	Apoptosis (↑)	228-230
GSIs	Notch (↓)	TRAIL (↑)	231,232

Bcl-2, B-cell lymphoma-2; Bax, Bcl-2 associated X protein; EGFR, epidermal growth factor receptor; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; miR, microRNA; GSI, γ-secretase inhibitor; ROS, reactive oxygen species; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

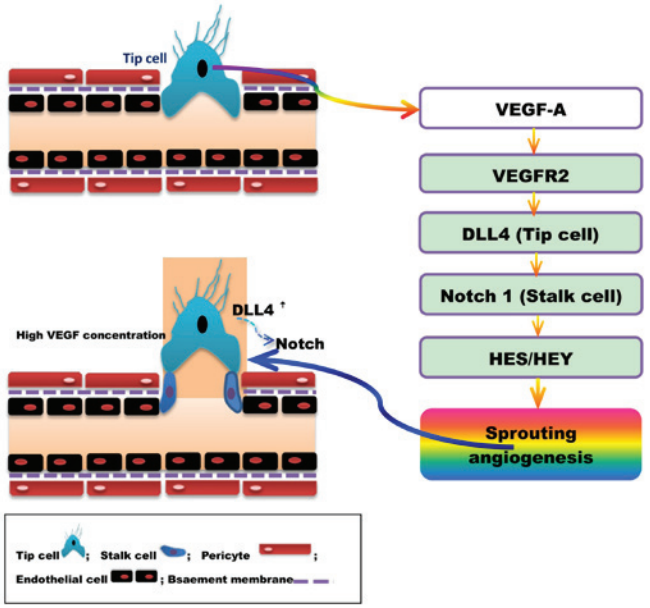

Figure 4. VEGF and DLL/Notch regulation of angiogenesis. VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; DLL4, Delta-like ligand 4; HES, hairy and enhancer of split; HEY, hairy and enhancer of split-related protein.

following Notch inhibition, however, these new blood vessels are dysfunctional (243,244).

Angiogenesis is a complex process regulated by numerous factors. The most well-known of these regulators is VEGF, which increases vascular permeability, promotes degradation of the extracellular matrix and migration and proliferation of vascular endothelial cells to induce angiogenesis. The expression of VEGF is controlled by multiple factors, including fibroblast growth factor, angiopoietins/Tie receptors, platelet-derived growth factor, TGF-β, hepatocyte growth factor, HIF-1α, forkhead box (Fox) c1/Foxc2, TNF-α, epidermal growth factor and matrix metalloproteinases (Table III).

VEGF, a growth factor expressed in vascular endothelial and other cells, acts directly on vascular endothelial cells to promote mitosis, induce proliferation and migration, maintain the integrity vessels and increase vascular permeability, and is thus critical for angiogenesis. VEGF-A is the most well-characterized of the VEGF family, and its receptor VEGFR2 is the primary receptor involved in angiogenesis (237). The mammalian Notch signaling pathway, comprised of four homologous Notch receptors (Notchl, Notch2, Notch3 and Notch4) and five cognate ligands (DLL1, DLL3, DLL4, Jaggedl and Jagged2) (254-256), is important for angiogenesis. High concentrations of VEGF induce DLL4 expression, thus, increasing Notchl expression on neighboring cells. The activation of DLL4-Notchl signaling pathways promotes angiogenesis (47,257,258). Studies have revealed that DLL4/Notch signaling mediates negative feedback; the expression of DLL4 may suppress the proliferation and migration of endothelial cells through the inhibition of VEGFR2 by HES-related protein 1 (259,260). VEGF, as a positive regulator of angiogenesis, initiates and promotes angiogenesis, whereas Notch signaling may negatively regulate the process to prevent endothelial cell hyperplasia and, in conjunction with VEGF, promote the formation of a well-differentiated vascular network (261-266).

Injection or nasal feeding of rats with human recombinant VEGF following focal cerebral ischemia in the middle cerebral artery promoted neovascularization of the ischemic area and the recovery of neurological function (267,268). In

Table III. Factors regulating VEGF expression.

Regulator	Mechanisms	References
Ang-1,2,3	Controls growth, maturation and stability of blood vessels; Ang-2, destabilizes.	245
FGFa/b	Promotes EC proliferation and migration; induces vascular branching.	237
PDGF	Recruits perithelial cells, vascular aging.	246
TGF-β	Bidirectional regulation: Low concentrations of TGF-β promote blood vessel formation, high concentrations of TGF-β inhibit EC growth, and promote smooth muscle cell differentiation and basement membrane formation.	247,248
HGF	Promotes EC proliferation, improves VEGF secretion in ECs and induces angiogenesis	249
HIF-1α	Interacts with NICD to increase the response to hypoxia and upregulates DLL4	250
Foxc1/Foxc2	Activates DLL4 expression	251
Angiopoietins/Tie	Increases expression of Ang-2/1	252,253

VEGF, vascular endothelial growth factor; Ang, angiopoietin; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor 1α; Fox, forkhead box; EC, endothelial cell; NICD, Notch intracellular domain; DLL4, Delta-like ligand 4.

addition, delayed treatment with VEGF alleviates brain injury, enhances endothelial cell proliferation and augments total vascular volume following neonatal stroke (269). Furthermore, the overexpression of VEGF in close proximity to intracerebral hemorrhage lesions in mice undergoing transplantation of F3 human neural stem cells (NSCs) facilitated differentiation and survival of the grafted human NSCs, and resulted in renewed angiogenesis in the host brain and functional recovery of mice (270). Studies have revealed that strategies to enhance angiogenesis following focal cerebral ischemia may improve recovery from stroke (271-274). The VEGF/Notch signaling pathway is the primary signaling pathway regulating angiogenesis following cerebral ischemia (47,275,276). VEGF and Notch are upregulated in brain tissue following cerebral ischemia, which may significantly promote angiogenesis in the ischemic region (277-280). Therefore, regulating the Notch signaling pathway may provide a potential strategy for the treatment of cerebrovascular diseases (281).

7. Notch signaling and BBB in cerebrovascular diseases

The BBB is a highly selective permeable barrier separating circulating blood from the brain extracellular fluid, to regulate the CNS microenvironment. The BBB is formed of a complex network of endothelial cells, astroglia, pericytes, perivascular macrophages and a basal membrane. Under physiological conditions, BBB integrity is primarily maintained by endothelial cells, through tight junctions, and the basal lamina; however, the structural and functional integrity of the BBB is markedly altered during CNS disorders, including neoplasia, ischemia, trauma, inflammation and bacterial and viral infections.

Cerebrovascular BBB dysfunction is closely associated with stroke, including intracranial hemorrhage and brain ischemia disorders. Endothelial cells are critical for numerous neurovascular functions, including angiogenesis, BBB formation and maintenance, vascular stability and removal of cellular toxins. Cerebrovascular endothelial cells interact with pericytes to maintain a stable cerebral circulation in the CNS. A number of studies have revealed that endothelial cell dysfunction in the CNS results in breakdown of the BBB and brain hypoperfusion, leading to neurodegeneration. It has been reported that disruption of Smad4 signaling, the central intracellular mediator of TGF-β signaling (14), in endothelial cells leads to the pathogenesis of intracranial hemorrhage and BBB breakdown (14,282), indicating that Smad4 maintains cerebrovascular integrity and that TGF-β/Smad signaling is involved in the pathogenesis of cerebrovascular dysfunction. Notch signaling is also critical in controlling BBB integrity via regulating the normal function of endothelial cells and pericytes. However, the underlying mechanisms regulating cerebral endothelial cell functions remain to be elucidated.

The Notch signaling pathway is involved in blood vessel integrity and BBB stability and function in the mammalian vasculature (75,283-285). *In vitro* studies have correlated BBB endothelial dysfunction with decreased Notch4 expression (286). Upon activation, the constitutively expressed endothelial cell membrane protein Notch4 appears to become primarily involved in the stability and growth of mature endothelium (287). Permanent ischemia leads to the redistribution of claudin decomposition fragments, zona occludens 1 and occludin protein from the membrane to the cytoplasm in BBB. Additionally, the GSI, DAPT protects against permanent ischemia-induced BBB damage, potentially via the modulation of Notch/NICD/calpastatin homeostasis pathway in vascular endothelial cells.

8. Conclusion and perspective

Increasing evidence indicates that Notch signaling is critical in the pathogenesis of stroke, exerting effects via the following underlying mechanisms: Neuroinflammation, oxidative stress, apoptosis, angiogenesis and BBB function. Thus, regulating Notch signaling may be an effective strategy for the prevention and treatment of cerebrovascular diseases.

Studies have demonstrated that the activation of Notch signaling is harmful and contributes to the pathogenesis of cerebrovascular diseases including stroke (20,98,202,204,288-290).

Acute inhibition of Notch signaling has been revealed to rescue cerebral hypoperfusion, reduce apoptosis in penumbra, decrease brain infarct size, elicit certain morphologic features, including neurogenesis and angiogenesis, associated with brain repair and functional recovery, and enhance vascular densities in penumbra in the neonatal rat brain following stroke (288).

However, activation of the Notch signaling pathway may have a neuroprotective role via enhancing endogenous neuroregeneration and brain arteriogenesis following stroke (51,291). In a murine transient global cerebral ischemia/reperfusion model, the neuroprotective effects of preconditioning were mediated via the Notch signaling pathway, and the expression of Notch1, NICD and HES-1 was upregulated (209). Notch signaling is widely accepted to be a fundamental pathway controlling cell fate acquisition through the regulation of adult neurogenesis. Studies have demonstrated that Notch signaling is crucial for the maintenance, proliferation and differentiation of NSCs in the developing brain (292,293). Notch signaling induces the neuronal expansion and differentiation following stroke (21). Increasing the expression level of Notch signaling components may facilitate intrastriatal transplantation therapy for ischemic stroke by promoting endogenous regeneration in the hippocampus (294). Promoting Notch signaling activity may facilitate increased arteriogenesis in a middle cerebral artery occlusion stroke rat model (54). In addition, Notch-induced rat and human bone marrow stromal cell grafts inhibited ischemic cell loss and abrogated behavioral deficits in chronic middle cerebral artery occlusion stroke rats (295).

Therefore, the results on the effect of Notch signaling on the pathogenesis of cerebrovascular diseases are contradictory. Notch signaling may be damaging, as it promotes inflammation, oxidative stress and apoptosis. However, the activation of the Notch signaling pathway may exert neuroprotective effects via enhancing endogenous neuroregeneration and brain arteriogenesis following stroke. What is the exact role of Notch signaling? Clarifying this question has potentially important implications for the treatment of cerebrovascular disease, and will provide novel strategies for future studies.

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