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How IL-9 signaling influences astrocytes and ultimately contributes to BBB disruption after ischemic stroke.

Parvin Mozafari[1], Mahdi Khan[2] ,Yamen Totonji [3], Sevara Abdulajanova[4], Hiba Mustafa[5]

1-Faculty of medicine, University of Georgia, Tbilisi, Georgia.

2-Faculty of medicine, University of Georgia, Tbilisi, Georgia.

3-Faculty of medicine, University of Georgia, Tbilisi, Georgia.

4-Faculty of medicine, University of Georgia, Tbilisi, Georgia.

5-Faculty of medicine, University of Georgia, Tbilisi, Georgia.

**Corresponding author: Parvin Mozafari1, Faculty of medicine, University of Georgia, Tbilisi, Georgia, Parvinmozaffari73@gmail.com, Phone number: +995-591096156.

** ORCID: Parvin Mozafari: 0009-0002-8107-2390, Mahdi Khan: 0009-0008-3330-0305, Yamen Totonji: 0009-0004-0304-580X, Sevara Abdulajanova: 0009-0005-3671-4384, Hiba Mustafa: 0009-0001-0372-6769.

Abstract

Despite the improvement of reperfusion therapies, acute ischemic stroke is still one of the main causes of death and long-term disability. Recovery is restricted by secondary neuronal injury, which is caused by neuroinflammation, edema and blood brain barrier (BBB) disruption. In this study, the PubMed and Google Scholar databases were searched for the following terms: “IL-9,” “astrocytes,” “BBB,” and “ischemic stroke.” The retrieved experimental studies and evidence-based syntheses (2016–2026) were performed and a narrative review was conducted. There is evidence that BBB breakdown occurs early (hours) as well as later through processes initiated by proteases/cytokines involving endothelial dysfunction, oxidative stress, ATP depletion, increased caveolae mediated transcytosis, and loss of tight-junction proteins (claudin-5, occludin) through VEGF-A/VEGFR2 signaling, eNOS activation and MMP-9–mediated degradation. Increased levels of IL-9 are found during stroke, astrocytes express receptors to IL-9 and IL-9 activated JAK/STAT3 signaling can promote reactive astrogliosis and astrocyte-derived VEGF-A (and possibly MMP-9), which further increases vascular permeability and BBB disruption. Experimental therapies that target IL-9 or downstream targets (STAT3, VEGF-A/VEGFR2, PLCγ–eNOS, MMP-9) have the effect of reducing VEGF-A, preserving tight junctions, and limiting damage to the BBB; GLP-1 receptor agonists (e.g., exenatide/Ex-4) have been found to inhibit inflammatory outputs of astrocytes without impairing beneficial microglial functions. These results identify and validate an underexplored therapeutic opportunity, the IL-9–astrocyte–VEGF-A axis, and point to multi-target, time- and cell-type-specific therapeutic approaches using biomarkers (such as MMP-9 levels, polymorphisms). Heterogeneity of the studies and publication bias reduces the translational potential and standardized longitudinal experimental and clinical validation is required.

Keywords: Ischemic stroke, Blood-brain barrier, neuroinflammation, Interleukin-9 signaling, Astrocytic end-feet.

Background

Acute ischemic stroke (AIS) among one of the common causes of death and long-term neurological disability worldwide. Regardless of serious improvements in reperfusion therapy, for instance IV thrombolysis and endovascular thrombectomy, progressive neuronal deterioration and functional impairment is still to be a challenge to treatment and rehabilitation results. Cerebral blood flow must be rapidly restored to decrease the cytotoxic effects of oxygen [1]. Nonetheless, edema formation, and neuronal death, neuroinflammation, and disruption of the blood brain barrier continue to cause secondary brain injury in a plethora of patients. Acute ischemic stroke, or also known as AIS, is immensely associated with poor functional after effect, it is imperative to comprehend the physiological and molecular mechanisms behind ischemic brain damage [2].

Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease

The blood brain barrier is a highly functional structure that maintains the central nervous system's homeostasis and appropriate neuronal activity. It regulates the flow of chemicals between the blood and brain parenchyma while protecting brain tissue from harmful substances in circulation. BBB, also known as blood brain barrier integrity, is primarily maintained by brain capillary endothelial cells, which are connected by tight junction proteins which are for example claudins, occludin, and related cytoplasmic proteins. Claudins like CLN-5, CLN-3, and CLN-12 are pivotal for the synthesis of tight junctions, whereas occluding maintains permeability of the barrier and junctional properties [1,2]. In addition to endothelial tight junctions mentioned, the BBB is functionally and structurally supported by pericytes embedded within the basement membrane and by astrocytic end-feet that surround the capillaries in the cerebrum. Pericytes generally regulate endothelial cell vascular permeability, angiogenesis, stability, and immune signaling, while astrocytic end-feet aid BBB integrity via metabolic support and secretion of signaling molecules that preserve function of tight junction. The basement membrane provides structural maintenance and helps communication among astrocytes, endothelial cells, and pericytes. Decreased anatomical integrity and high permeability of the barrier are one of the characteristics of Blood brain barrier impairment which makes the primary pathogenic physiognomy of ischemic stroke and other neuroinflammatory disorders [3].

Phased Blood–Brain Barrier Disruption in Ischemic Stroke: Implications for Therapy.

The endothelial dysfunction, metabolic stress, oxidative damage, and inflammatory signals cause dismantling of the BBB rapidly following an ischemic stroke, instantly within hours of the degeneration [3]. Furthermore, insufficient synthesis of ATP which refers to adenosine triphosphate during ischemia impairs the brain’s habitat and complicates to voluminous apoptosis and cellular damage. Disruption of the brain barrier embitters neuronal damage by metabolic imbalance, facilitating vascular edema, excitotoxicity, peripheral infiltration of immune cells in the body, and hemorrhagic metamorphosis. During the initial stages of the brain injury, characteristics such as enhanced caveolae mediated vesicular transport across endothelial cells make it easier for proteins and immunological mediators to enter the brain parenchyma exhibiting its ramification [3].

Role of Crosstalk between Glial Cells and Immune Cells in BBB Damage and Protection after Acute Ischemic Stroke

With the molecular processes that lead to the eradication of Blood brain barrier post ischemic injury are TJP degradation, inflammation, immunological activation, and trans-endothelial hyperpermeability. Secondary brain injury and disintegration of the BBB have been notably associated with immunologic cytokines, ROS or reactive oxygen species, matrix metalloproteinases or MMPs, chemokines, and vascular endothelial growth factor A-VEGF-A, Endothelial nitric oxide synthase

mediates VEGF-A signaling through vascular endothelial growth factor receptor-2-VEGFR2, which causes increase in vascular permeability of these neuroinflammatory conditions. Post AIS, necroptosis of endothelial cell could be due to inflammatory cytokines such as TNF- α aka tumor necrosis factor-alpha, which altogether these cytokines and chemokines play a significant role in the pathogenesis during the neuroinflammatory states of brain disruption [4].

Following ischemic injury, disruption of BBB discussed occurs in two phases. The early phase that forms within hours is driven by endothelial dysfunction, oxidative stress, ATP depletion, ROS production, and increased transcytosis/caveolae-mediated transport, complicating increased permeability before catastrophic structural damage ensues [4]. The second or later phase involves activation of matrix metalloproteinases, especially MMP-9, cytokine and chemokine release (including TNF-α), degradation of tight junction proteins such as claudin-5 and occluding and VEGF-A/VEGFR2 signaling mediated by endothelial nitric oxide synthase. These processes promote endothelial cell necroptosis, increase vascular permeability, secondary brain injury, and the progression of ischemic stroke and other neuroinflammatory disorders [4].

Implications of MMP9 for Blood Brain Barrier Disruption and Hemorrhagic Transformation Following Ischemic Stroke. Popular mediators particularly like matrix metalloproteinases-MMP-2& MMP-9 have been responsible for the BBB impairment, since MMPs breakdown basal membrane proteins, extracellular matrix molecules and the cerebral vasculature become physiologically erratic [5]. MMP-9 notably contributes to damage of the brain barrier and vasogenic edema by degrading type IV collagen found in the basement membrane, fibrinogen in the vascular basement membrane and fibronectin. Furthermore, these matrix metalloproteinases 2 and 9 are noted to be responsible for stroke constituting edema synthesis, neuroinflammation, and poor neurological results. In addition to having a role in early ischemic injury, MMP-9 specifically has turned up as an auspicious biomarker for the initial detection and prognosis of acute ischemic stroke [5].

Blood-brain barrier dysfunction and recovery after ischemic stroke

In the pathogenesis of ischemic stroke, glial cells have been noted to have a major role. These cells maintain most importantly the metabolic and structural integrity of neurons, regulate synaptic activity and support the growth and homeostasis of the central nervous system under normal conditions. Nonetheless, to coordinate neuroinflammatory responses, glial cells are mediated consequent to ischemic injury, therefore forming chemokines, neurotrophic factors, cytokines, chemokines, and DAMPs which damage associated molecular pattern molecules. Endothelial cells, astrocytes, oligodendrocyte precursor cells, microglia, and invasive immune cells all have a brunt on the brain barrier integrity as well as the after-stroke granulation or healing processes [6].

Activation and Role of Astrocytes in Ischemic Stroke

Astrocytes are among the most important glial cells involved in ischemic stroke. They are broadly specified into fibrous astrocytes settled in white matter, protoplasmic astrocytes arranged in gray matter, and radial astrocytes found near the ventricles. Astrocytes are popularly known for regulating

perfusion of the brain, stabilizing and maintaining the barriers integrity, and providing metabolic and neurotrophic support and of course aiding and controlling oligodendrocytes that myelinate the CNS and neurons. Approaches in single-cell RNA sequencing and spatial transcriptomics have identified remarkable astrocytic heterogeneity and specialization depending on regional brain localization [7].

Astrocytes and Inflammatory T Helper Cells: A Dangerous Liaison in Multiple Sclerosis

During ischemia and neuroinflammatory disorders, astrocytes experience morphological and functional changes recognized as reactive gliosis. Astrocytes that are active exhibit numerous expressions of molecular markers involving Vimentin, IL-17R, glial fibrillary acidic protein, S100B, complement component C3, superoxide dismutase 1, and tropomyosin receptor kinase B. Additionally these astrocytes secrete neurotoxic and neuroprotective mediators. On one hand, they secrete neurotrophic factors that base neuronal survival, brain regeneration, and tissue adjustment. Moreover, they produce proinflammatory cytokines and chemokines that recruit leukocytes and inflammatory T helper cells into the CNS, related to secondary brain injury and BBB disruption [6,7].

Glial Cells: Role of the Immune Response in Ischemic Stroke

Microglia is the main immune cell of the CNS which is an important regulator of post stroke neuroinflammation. Animated microglia secrete various cytokines and chemokines that effect immune cell recruitment and inflammatory signaling. Depending on its activation state, microglia may have both beneficial and negative impacts. Anti-inflammatory cytokines and neurotrophins secreted by microglia can credit blood brain barrier repair and neurological recovery, whereas biased inflammatory activation may provoke tissue damage [8]. Based on studies it's shown that diminishing neutrophilic infiltration and microglial activation violate to preservation of blood brain barrier solidity and improves neurological functional outcomes post stroke.

The glucagon-like peptide-1 receptor agonist reduces inflammation and BBB breakdown in an astrocyte-dependent manner in experimental stroke

Therapies that target glial inflection and blood brain barrier security have presented miraculous results in today's experimental stroke models. GLP-1 or glucagon-like peptide-1 receptor activators have diminished TJP degradation through its neuroprotective mechanism, additionally maintaining blood brain barrier stability in both traumatic and ischemic brain injuries along with masking microglial activation. Moreover, OPC transplantation has been reported to decrease the volume of infarcts, stabilize blood brain barrier probity, reduce brain edema, and enhance neurological recovery in experimental acute ischemic stroke. These above findings indicate the therapeutic ability of targeting brain cells such as glial cells and its barrier associated signaling pathways involved in the brain stroke [9].

IL-9 Biology

Interleukin 9 is a cytokine which is produced by T helper 9 cells, it can be produced by T helper 2 and 17, regulatory T cells, mast cells, and innate lymphoid cells. IL-9 binds to the IL-9 receptor and gets activated, which activates JAK/STAT pathways that control immune cell growth, survival, and inflammatory processes [8,9]. It is linked to anti-parasite immunity and allergic inflammation because it has particular effects on mucus production and mast cells. IL-9 is now known as a dependent mediator within the immune system with its unique anti-inflammatory and pro-inflammatory functions. To sum it up, these cytokines activity impact different processes including tumor immunity, inflammation of the tissues, autoimmunity, and neuroimmune regulation, making IL-9 a very essential cytokine within the research of immunology [9].

Why IL-9–astrocyte interaction is important

Renowned evidence suggests that brain cells like astrocytes express IL-9 receptors and respond to the cytokines signals during neuroinflammation seen in strokes for instance. In ischemic brain stroke, IL-9 astrocyte linkage is known to modulate astrocyte invigoration, eventually decreasing accumulated neuroinflammation meanwhile providing repair, support, and neuroprotective mechanism [10]. This interaction is presumably important because this plethora of astrocyte-based inflammation has a role in secondary brain injury response post stroke, including edema formation, neuronal apoptosis, and BBB intrusion. In contrast, astrocytes being regulated properly contribute to metabolic and angiogenesis support, synaptic regeneration, and neuronal repair. Therefore, IL-9 signaling stimulates the homeostasis between protective and harmful functions of astrocytes. Comprehending the mechanism of IL-9 astrocyte axis is thought to provide vision into immunoenhancing therapeutic techniques targeting to improve recovery and limit neurological ischemic damage[10].

Methodology

The aim of this narrative review was to summarize and critically analyze the existing evidence of the role of IL-9 astrocyte interactions in BBB after ischemic stroke. Literature search was performed on an online database, PubMed, google scholar to search the research papers published between the year 2016 and 2026. While the key words used for the search included “IL-9,” “interlulin-9,” “Astrocytes,” “blood-brain barrier,” “BBB,” “ischemic stroke”. This narrative review utilized studies for human and experimental research, and systemic review and meta-analysis that were related to the role of IL-9 astrocyte interaction in the blood-brain barrier (BBB) after ischemic stroke. Studies that were not directly related to the topic, non-peer-reviewed sources and replicated studies were excluded. From the selected studies information was extracted and analyzed to find the new findings, suggested mechanisms and emerging trends regarding IL-9 astrocytes interactions in BBB after ischemic stroke.

Discussion

The blood-brain barrier (BBB) was first identified in the start of the 20th century by Lewandowsky and other workers, due to the absence of CNS pharmacological effects of intravenously administered

bile acids and ferrocyanide. BBB plays a crucial role in the maintenance of CNS homeostasis and normal neuronal function [1,12]. The blood-brain barrier (BBB) acts as a selective membrane that restricts permeability using occluding tight junctions. Major drivers behind the occluding tight junctions are claudins and occludin. During the event of ischemia, BBB breakdown is a key pathological consequence. Astrocytes are the most abundant neuronal cell type in the brain that gets activated during the event of stroke. Key roles of astrocytes involve ion hemostasis and metabolism as well as release of neurotransmitters through exocytosis and ion channels. Most importantly, it maintains cerebral blood flow and blood brain-barrier. This discussion is based on thorough analysis of various comprehensive literature that establish astrocytes as key regulators of both BBB disruption and repair, while vascular endothelial growth factor (VEGF-A) emerges as a master coordinator of these processes as well as how interleukin-9 and astrocytes interact with one another and their role in compromising blood-brain barrier integrity after hypoxic cerebral infarction, with particular attention to possible intervention strategies [11,12].

IL-9 and Astrocyte Mediated BBB Disruption

In the event of an ischemic stroke, brain injury can worsen by the body's immune signals, not just by starving neurons of oxygen, but by breaking down the barrier that protects the brain. One key player in this process is IL-9, an immune signaling molecule. In stroke patients, IL-9 levels rise in the blood [12]. The brain's support cells, astrocytes, carry receptors for IL-9. In response, they pump out more VEGF-A, a molecule the body normally uses to grow new blood vessels. Recent studies have highlighted the link between reactive astrocytes and BBB breakdown. In the event of lesion pathogenesis, astrocyte expressions of angiogenic factors include VEGF-A and its regulator HIF-1α. Existing literature suggests activation of astrocytes is strongly related to JAK/STAT3 pathway. JAK/STAT3 serves as one of several pathways capable of inducing VEGF-A expression in astrocytes, especially under inflammatory conditions. Studies have identified VEGF-A expression is induced on activation of the JAK/STAT3 signaling pathway in reactive astrocytes, which results in increased vascular permeability and blood-brain barrier breakdown [13].

STAT3 is the key transcription factor behind the cytokine signaling pathway responsible for mediating the interleukin-6 (IL-6). STAT3 activation initiates phosphorylation at the tyrosine 705 (Y705) residue, which promotes its dimerization, nuclear translocation, and DNA-binding activity. In many signaling pathways, STAT proteins are phosphorylated by JAK family kinases, including JAK1, JAK2, JAK3, and TYK2, which become activated through trans-phosphorylation ligand-induced receptor oligomerization [14].

STAT3 also serves as a critical downstream effector of vascular endothelial growth factor (VEGF). VEGF primarily signals through VEGF receptor-2 (VEGFR-2/KDR), triggering STAT3 activation and subsequent regulation of genes involved in endothelial cell activation, vascular inflammation, and other important biological functions [15]. Downregulation of VEGF-A is crucial to prevent disruption and integrity of the blood–brain barrier (BBB). A potential mechanism underlying this effect involves the direct link between IL-9 release and increase in the level of VEGF-A in astrocytes. The pooled

analysis identified that blocked IL-9 using neutralizing antibodies in animal models, VEGF-A levels dropped, the tight junction proteins were preserved, and BBB damage was reduced. Blocking this chain, particularly at the induction of IL-9 step, could serve as a crucial strategy for protecting the brain in the initial phases of stroke [14,15].

VEGF-A and the Molecular Mechanisms of BBB Disruption

VEGF-A has become increasingly recognized as a major driver of blood-brain barrier disruption during ischemic stroke. VEGF-A damages the barrier by breaking down the tight junction proteins that hold it together. When a stroke shuts down blood flow, astrocytes in the damaged area get activated and start releasing VEGF-A. This VEGF-A spreads through the tissue and binds onto a receptor around blood vessel cells called VEGFR2. VEGF-A binding to receptor, starts the chain inside the cell [16]. Phospholipase C gamma is the first protein to get activated on the VEGF-A binding to the receptor. This protein further activates endothelial nitric oxide synthase or eNOS. eNOS downregulates claudin 5 and occluding, both proteins that are key drivers in maintaining the integrity of the blood brain barrier. Through a series of well-connected molecular events, the initial ischemic insult progresses to disrupt blood-brain barrier, resulting in increased vascular permeability [16].

Researchers performed experiments to test the functionality of this pathway and its relevance. It was performed on mice with autoimmune encephalomyelitis, which is a pathology that involves destruction to the nervous system in ways like stroke [16]. Blocked eNOS via the drug cavtratin, resulted in prevention of developing paralysis, and the tissue damage was much less severe than in untreated animals. This finding suggests that if you block eNOS during an actual ischemic stroke, you might be able to protect the blood brain barrier from breaking down in the first place. Since both VEGFR2 and eNOS are required for this pathway to destroy tight junction proteins, there are multiple places where drugs could step in to stop the process [17].

Hypoxia and HIF-1α: The Oxygen-Sensing Problem

HIF-1α activation following ischemic injury induces the expression of pro-inflammatory mediators and vascular endothelial growth factor-A (VEGF-A). Studies have already established that the JAK2/STAT3 signaling pathway further enhances VEGF-A production. These pathways have significant crosstalk, whereby increased VEGF-A expression leads to downstream signaling activity, creating a positive feedback loop that amplifies neuroinflammation, angiogenesis, and blood–brain barrier (BBB) dysfunction. As this feedback mechanism becomes established, pathological signaling is progressively reinforced, making it difficult to potentiate a positive therapeutic effect. Combination therapies or multi-target treatment strategies may be required to achieve meaningful neuroprotection and preservation of BBB integrity [18].

Matrix Metalloproteinase-9 and Complementary Degradation Mechanisms

Alongside VEG-F, MMP-9 is a key enzyme that directly breaks down the structural proteins claudins and occludin that hold the barrier together. Activation of MMPs degrades components of the BBB

causing the disruption of the membrane. MMP-9 levels rise in several CNS conditions and result in increased permeability. Stroke patients are equally vulnerable to increased MMP-9 in their blood, which makes it useful as a marker. High MMP-9 is a key indicator that barrier integrity is compromised. Multiple experimental studies suggest expression of tissue inhibitors of matrix metalloproteinase (TIMP)-1that increase along with MMP-9. MMP-9 comes in different genetic versions depending on your ethnic background. This might explain why some patients experience worse barrier breakdown than others. The reality is that the barrier is getting attacked from two directions at once: through inflammatory signaling and through direct protein destruction. Any effective treatment has to tackle both problems [18].

Astrocytes: Bifunctional Roles in BBB Disruption and Recovery

Then there's the astrocyte problem, which makes things even more complicated. During a stroke, when blood flow stops and then comes back, astrocytes dump inflammatory chemicals (MCP-1, CXCL-1) into the tissue that make inflammation worse and tear up the barrier. Initially, it makes sense to shut down this inflammatory response. But it's not quite straightforward. Astrocytes aren't just causing problems [19]. They're also doing essential cleanup work. They remove dead cells and debris from the damaged area, and they release protective molecules that neurons need to survive and recover. If you clamp down on astrocytes too hard, it negatively impacts the healing process instead of helping it. It ends up detrimental to the recovery. The solution requires balance: reduce inflammatory output while maintaining protective capacity [19].

GLP-1 Receptor Agonists: Selective Multi-Target Intervention

Here's where GLP-1 agonists come in. GLP-1 receptors are scattered all over the brain on different cell types: blood vessel cells, neurons, astrocytes, immune cells. This is actually useful because it means a single drug can target multiple problems at once instead of needing several different medications. Exenatide is one example. The research shows it does several things: it makes blood vessel cells stronger and more resistant to damage, it protects neurons when oxygen is cut off, it reduces how leaky the barrier becomes and prevents immune cells from flooding in, and it tells astrocytes to dial back their inflammatory output [17,18,19]. What's valuable about exenatide is that it stops the harmful VEGF-A production while keeping astrocytes alive and functional. That's a smart approach because you're not just nuking the immune system indiscriminately. You're being selective about what you're suppressing and what you're preserving.

Moreover, GLP-1R agonists in post middle cerebral artery occlusion lowers microglia activity and neutrophil infiltration, it means that there is a coordinated anti-inflammatory effect over multiple glial. Nevertheless, approaching evidence suggests important mechanistic small differences in GLP-1R signaling [19]. At the same time Ex-4 effectively decreases astrocyte derived inflammatory factors, new findings indicate that GLP-1R activation may not inhibit lipopolysaccharide or ischemia induced expression of microglia derived pro inflammatory cytokines, implying a selective anti-inflammatory

action that is astrocyte specific rather than immunosuppressive. This distinction may be profitable, as it allows preservation of microglial neuroprotective functions which is debris clearance and growth factor secretion while suppressing harmful inflammatory outputs. Further investigation into the cell type specificity of GLP-1R agonist actions will be important for improving their therapeutic use in acute stroke [19].

The Temporal Complexity and Dual Roles of Glial Cells in Stroke Recovery

Post stroke neuroinflammation includes arranged stimulation of multiple glial populations such as microglia, astrocytes, and oligodendrocytes each of them shows context dependent pro inflammatory and neuroprotective activity. Microglia, for example, could release inflammatory cytokines which are detrimental functions and clear cellular debris while secreting neurotrophic factors which are a neuroprotective function. Similarly, astrocytes exist as pro inflammatory A1 like phenotypes and anti-inflammatory A2 like forms, with the balance between these states seriously determining recovery orbits. Preceding experiments to therapeutically block microglial invigoration have failed, probably because such large suppression eliminates helpful microglial functions and harmful ones, resulting in harmed debris clearance and decreased growth factor support during recovery [19,20]. This principle that extensive inhibition of glial activation impairs recovery dispute for rigor therapeutic approaches that selectively conceal harmful products while preserving valuable functions. It is noteworthy that the GLP-1R agonists seem to selectively block the production of inflammatory mediators from astrocytes and leave the overall function of the glia intact, also suggests the principle of selective suppression [20].

One of the particular importance in the post stroke response are the oligodendrocytes, which play a key role in the recovery of myelin and axonal reconstruction, which are essential for functional recovery. However, myelin proteins could be pro-inflammatory, and so it is important that the activation of oligodendrocytes and their subsequent drop of myelin is regulated in time and intensity to promote repair, but not to promote maladaptive autoimmunity. A temporal switch between the stimulation of the glia and pro inflammatory responses that could be important for immune clearance, followed by a shift towards pro repair phenotypes suggests the relevance of time dependent therapeutic targeting that reflects the dynamic post stroke microenvironment [20].

Integration and Future Therapeutic Directions

There is a complex network of molecular signaling, glial stimulation and temporal dynamics involved in IL-9 astrocyte interaction and blood brain barrier destruction in ischemic stroke [20]. Active astrocytes produce VEGF-A that travel down the cascade towards VEGFR2 PLCγ eNOS signaling in endothelial cells, resulting in degradation of TJP and invigoration of MMP-9. Microglial and astrocytic activation plays a role countering immunosuppressive approaches and support destructive mediations that decrease harm. Beneficiary therapeutic accesses can be used to effectively target approaches that: Dissolve pathological production of VEGF-A by active astrocytes; Inactivate VEGF-A eNOS axis in

endothelial cells to prevent TJP destruction; Reduce MMP-9 response to secure TJP solidity; and Inactivate agents that specifically target astrocyte derived inflammatory cytokines without affecting positive glial functions. The clinical explanation of these findings will require accurate temporal mapping of blood brain barrier dysfunction in patients, perception of biomarkers that anticipate individual ability to severe blood brain barrier breakdown such as MMP-9 polymorphisms, and proper testing of mix approaches that explicit multiple complementary pathways. Multi target strategy has potential benefits for reducing secondary injury and long-term functional outcomes in ischemic stroke patients [20].

Conclusion

The evidence reviewed in this study provides an overview of the integrity and shows how dysregulated astrocyte responses can exacerbate vascular damage following cerebral ischemia. A critical event in the pathogenesis of ischemic stroke is the blood-brain barrier disruption, which is associated with the development of cerebral edema, inflammatory response, and further neuronal damage. These findings provide further support for previous studies by providing additional insight into the role of IL-9 in astrocyte function, underscoring its importance in regulating BBB integrity following cerebral ischemia. IL-9, enhancing inflammatory signaling and stimulating astrocytes-mediated release of vascular endothelial growth factor -A (VEGF-A) and other damage mediators, may contribute to ischemic stroke pathology. Additionally, many other mechanisms such as glial-immune cell interactions, oxidative stress, neurovascular unit dysfunction and matrix metalloproteinase-9(MMP-9) activation, were identified as significant contributors to BBB disruption after stroke.

Experimental evidence supports a mechanistic pathway where IL-9 acts as an upstream inflammatory mediator that promotes astrocyte activation. Activated astrocytes up-regulate the production of factors such as vascular endothelial growth factor (VEGF-A) and matrix metalloproteinase-9 (MMP-9) which lead to the disruption of endothelial tight junction proteins and enhancing blood brain barrier (BBB) permeability. Taken together, these findings suggest that neurovascular injury after ischemic stroke may involve a pathway that can be explained by the sequence of IL-9 elevation, activation of astrocytes, release of VEGF-A and MMP-9, disruption of tight junctions, and BBB breakdown. IL-9 has received limited attention in stroke research, although the function of mediators like MMP-9 and VEGF-A in BBB dysfunction has been extensively studied. Based on current evidence, IL-9 seems to be an emerging central regulator of BBB damage by astrocytes. As a result, it is a promising topic and target for further research. Overall, this has relevance in the context of therapeutic strategies for improving neurologic recovery and decreasing injury of the blood-brain barrier during ischemic stroke, by targeting IL-9 signaling and astrocyte-mediated inflammatory pathways. Despite this, the knowledge obtained to date has been obtained from experimental studies, and the exact molecular mechanisms by which the action of IL-9 on astrocyte behavior and BBB integrity occur remain poorly understood.

One strength of the present review is that the process of evidence synthesis was comprehensive and systemic. But there are some limitations one should pay attention to while interpreting the results of the present review. At the same time, it should be considered that heterogeneity cannot be overlooked,

as the studies included in this review exhibited heterogeneity from a methodological perspective in terms of study design, models used and outcome measures. Moreover, publication bias is not excluded, as this review included peer-reviewed scientific literature. Further experimental and clinical studies are needed to assess long-term effects and to unify the methodology of the studies. Thus, research investigating molecular pathways associated with IL-9 therapy for ischemic stroke would add to the validity of the existing evidence. In summary, the studies described above provide evidence in favor of the assumption that IL-9 astrocyte interaction plays a crucial role in the BBB damage caused by ischemic stroke. However, additional research is required to define the role of IL-9 in stroke pathogenesis and to determine whether targeting IL-9 signaling might serve as a promising treatment strategy for preservation of BBB integrity. These data enhance knowledge of IL-9-astrocyte interaction, which might be an important mechanism of BBB impairment caused by stroke.

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