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Review article

Focusing on claudin-5: A promising candidate in the regulation of BBB to treat ischemic stroke

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ABSTRACT

Claudin-5 is a tight junction (TJ) protein in the blood-brain barrier (BBB) that has recently attracted increased attention. Numerous studies have demonstrated that claudin-5 regulates the integrity and permeability of the BBB. Increased claudin-5 expression plays a neuroprotective role in neurological diseases, particularly in cerebral ischemic stroke. Moreover, claudin-5 might be a potential marker for early hemorrhagic transformation detection in ischemic stroke. In light of the distinctive effects of claudin-5 on the nervous system, we present the elaborate network of roles that claudin-5 plays in ischemic stroke. In this review, we first introduce basic knowledge regarding the BBB and the claudin family, the characterization and regulation of claudin-5, and association between claudin-5 and other TJ proteins. Subsequently, we describe BBB dysfunction and neuron-specific drivers of pathogenesis of ischemic stroke, including inflammatory disequilibrium and oxidative stress. Furthermore, we summarize promising ischemic stroke treatments that target the BBB via claudin-5, including modified rt-PA therapy, pharmacotherapy, hormone treatment, receptor-targeted therapy, gene therapy, and physical therapy. This review highlights recent advances and provides a comprehensive summary of claudin-5 in the regulation of the BBB and may be helpful for drug design and clinical therapy for treatment of ischemic stroke.

Abbreviations: 5α-DHP, 5α-dihydroprogestrone; ABC, ATP-binding cassette; AF6, ALL-1-fused gene from chromosome 6; ALL, acute lymphoblastic leukemia; AMPAR, amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor; Ang-1, angiopoietin-1; AP-1, activator protein-1; BBB, blood-brain barrier; Bcl, B-cell lymphoma; BCSFB, blood-CSF barrier; BEC, brain endothelial cell; BTB, blood-tumor barrier; cAMP, 3′-5′-cyclic adenosine monophosphate; Cav-1, caveolin-1; CNS, central nervous system; COX, cyclooxygenase; C-P, Catalpol and Puerarin; CSF, cerebrospinal fluid; CXCL12, C-X-C-chemokine ligand 12; EA, electroacupuncture; ECL, extracellular loop; ECM, extracellular matrix; eNOS, epithelial NO synthase; EPO, erythropoietin; ER, estrogen receptor; ERK1/2, extracellular signal-regulated kinases 1/2; FoxO, forkhead box O; GAP-43, growth associated protein 43; GDNF, glial cell line-derived neurotrophic factor; GLUT, glucose transporter; GPER-1, G protein-coupled estrogen receptor 1; GSH, glutathione; H/R, hypoxia/reoxygenation; HCV, hepatitis C virus; HIF-1α, hypoxia-inducing factor-1α; HBMEC, human brain microvascular endothelial cell; HO-1, hemeoxygenase-1; I/R, ischemia/reperfusion; ICH, intracerebral hemorrhage; IgG, immunoglobulin G; IL, interleukin; iNOS, inducible NO synthase; IVIg, intravenous immunoglobulin; JAM, junctional adhesion molecule; KLF6, kruppel-like factor 6; MAGI, membrane-associated guanylate kinase inverted; MCAO, middle cerebral artery occlusion; MCP-1, monocyte chemoattractant protein-1; miRNA, microRNA; MMP, matrix metalloproteinase; MUPP1, multi-PDZ domain protein 1; NF-κB, nuclear factor-κB; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; NVU, neurovascular unit; OGD, oxygen glucose deprivation; PALS, protein associated with Lin seven; PAR, protease-activated receptor; PARP, poly(ADP-ribose)polymerase; PATJ, PALS-1 associated TJ protein; PDZ, PSD95/Disc-large/ZO-1; PKA, protein kinase A; PSD95, post-synaptic density 95; RhoK, Rho kinase; ROS, reactive oxygen species; rt-PA, recombinant tissue plasminogen activator; SGLT, sodium-glucose cotransporter; siRNA, short interfering RNA; SOD, superoxide dismutase; TEER, transendothelial electrical resistance; TGF-β, transforming growth factor-β; TJ, tight junction; TMP, 2,3,5,6-tetramethylpyrazine; TNF, tumor necrosis factor; VE, vascular endothelial; VEGF, VE growth factor; ZO, zonula occludens.

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Contents

1. Introduction

Stroke is the primary cause of disability, producing immense health and economic burdens in adults worldwide, and it affects approximately 795,000 people annually (Benjamin et al., 2017). Stroke creates a loss of brain function due to a disturbance in the blood supply to the brain. This disturbance is caused by occlusion of a vessel due to a blood clot or by a bleeding vessel. Stroke is associated with a variety of complications, which occur early and late after stroke, such as cerebral edema, hemorrhagic transformation, spreading depolarization, seizures and epilepsy (Schoknecht et al., 2015). Accordingly, stroke can be classified into two categories: ischemic stroke and intracerebral hemorrhage (ICH). In both cases, the affected area of the brain cannot function normally, which may result in an inability to move one or more limbs on one side of the body, a failure to understand or formulate speech, or visual impairment on one side of the visual field (Muir, 2016). Because ischemic stroke is more common than ICH in all cases, we pay attention to the former throughout this review.

Ischemic stroke results from a transiently or permanently restricted blood flow to a portion of the brain, which results in an irreversibly damaged ischemic core and a surrounding region of potentially recoverable tissue. The remaining hypoperfused tissue exhibits altered mechanisms of blood flow autoregulation, which is known as the penumbra (Moustafa and Baron, 2008). Academically, the penumbra can be theoretically salvaged if reperfusion therapy and pharmacotherapy are administered as early as possible following the stroke, which prevents continued growth of the ischemic core and progressively worsening neurological outcomes. Significant progress has been made in dissecting neuron-specific drivers of the pathogenesis of ischemic stroke, including neuroinflammation, oxidative stress, neuroapoptosis, mitochondrial dysfunction, excitotoxicity, and ionic imbalance. As our understanding has advanced, we now appreciate that ischemic stroke not only involves neuronal dysfunction but is also orchestrated by the intricate interplay among many cellular players (Petrovic-Djergovic et al., 2016). This network of cellular players now is commonly referred to as the neurovascular unit (NVU), primarily comprising the brain endothelial cells (BECs), pericytes, and astrocytic end-feet, which can interact with surrounding neurons, microglia, and extracellular matrix (ECM) (del Zoppo, 2009). NVU helps to explain blood-brain barrier (BBB) induction processes and maintenance of BBB integrity and permeability in health and disease (Greene and Campbell, 2016).

The BBB is an active interface between the circulation and the central nervous system (CNS), maintaining the neural microenvironment with a dual function: the barrier function restricts transport of potentially toxic or harmful substances from the blood to the brain, and the carrier function is responsible for the transport of nutrients to the brain and removal of metabolites. The BBB plays a key role in clinical practice for ischemic stroke as well. On one hand, the permeability of the BBB is increased during ischemic stroke, with an initial and late opening of the BBB (Saraiva et al., 2016). On the other hand, the relative impermeability of the barrier limits many beneficial drugs from reaching the CNS in therapeutically relevant concentrations, making the BBB one of the major impediments to the treatment of ischemic stroke.

Several promising targets have been indicated to improve long-term recovery after stroke, such as proteins involved in membrane trafficking, particularly Rho GTPases Rac and RhoA (Posada-Duque et al., 2014; Stamatovic et al., 2017). Previous studies have demonstrated that Rac1 activity is involved in long-term recovery from neurodegeneration after cerebral ischemia, as evidenced by treatment with a pharmacological inhibitor of RhoA that inhibits the activation of the neurodegeneration cascade (Johanna et al., 2010). Moreover, there are another two pivotal kinds of regulation,

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