Commentary

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Early and enduring: Targeting the endothelium for blood-brain barrier protection

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Abstract

The disruption of the blood-brain barrier marks a pivotal early pathological event in ischemic stroke that significantly contributes to subsequent permanent damage. Here we delve into the ramifications of a study conducted by Xu and colleagues, which underscores the essential role of the protein peroxiredoxin-4 in cerebrovascular endothelial cells. Peroxiredoxin-4 was shown to preserve blood-brain barrier integrity during the early stages after cerebral ischemia and reperfusion, ultimately leading to improved long-term outcomes.

Keywords

Endothelial cell, inflammation, ischemic stroke, peroxiredoxin-4

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The blood-brain barrier (BBB) is a specialized microvascular structure in the brain that orchestrates the transfer of substances between the bloodstream and the brain, ensuring a stable microenvironment for optimal neuronal function.[1] This dynamic interface between the CNS and the periphery modulates the two-way traffic of fluids, solutes, and cells. Breakdown of the BBB—characterized by a loss of structural integrity and normal function—is a notable pathological hallmark of ischemic stroke, which exacerbates injury progression, increases hemorrhage risk, and predicts poor patient outcomes.[1,2] At present, there are no established BBB protective agents in the therapeutic landscape for stroke management, underscoring the urgency to decipher the biological underpinnings of BBB damage following ischemic stroke.

Xu et al. have now discovered that the antioxidant enzyme peroxiredoxin-4 (Prx4) in cerebrovascular endothelial cells (CECs) acts as an intrinsic defense mechanism against BBB damage, the entry of deleterious peripheral cells, cerebrovascular inflammation, irreversible loss of brain tissue, and long-term behavior deficits.[3] The study's pioneering methodology leveraged cell-specific knockout and overexpression mouse models that confine genetic modifications to the endothelial layer. While the absence of Prx4 did not significantly affect gross anatomy or physiology of the microvasculature in normal brain, the lack of basal Prx4 expression rendered the endothelium more susceptible to ischemia/reperfusion injury. On the other hand, transgenic overexpression of Prx4 within these cells leads to improved functional recovery and long-term preservation of brain tissue.[3] This discovery sheds light on the potential of endothelial Prx4, positioning it as an encouraging target for future investigations into stroke treatment modalities.

Peroxiredoxins (Prxs) constitute a critical family of antioxidant enzymes within mammalian cells, featuring six distinct isoforms (Prx1-Prx6). Prx4, a pivotal member of the peroxiredoxin family, predominantly resides within the endoplasmic reticulum (ER) and plays an essential role in antioxidant defense, protein

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folding, cell signaling, and comprehensive cellular protection.[4] The study conducted by Xu et al. unveils that the molecular activities of Prx4 play a critical role in maintaining the BBB's integrity, accomplishing this by potently inhibiting the phosphorylation and activation of myosin light chain (MLC) and obstructing actin polymerization, the formation of stress fibers, and the translocation of junctional proteins after cerebral ischemia/reperfusion.[3] Consequently, Prx4 plays a significant role in alleviating damage to the BBB, cerebral inflammation, tissue injury, and chronic neurological deficits that emerge from the compromised BBB integrity after stroke (Figure 1). Nonetheless, the specifics of how Prx4's interactions with mitochondria contribute to BBB protection remain an area for further exploration. Previous studies have illuminated a mitochondrial mechanism in CECs that regulates the permeability of the BBB.[5] Mitochondrial dysfunction can manifest as mitochondrial fusion, mitochondrial membrane permeability, transitions, pores, and dynamic changes, which lead to NOD-like receptor protein 3 inflammasome activation, intrinsic apoptosis, oxidative stress, and ER stress.[6] Evidence suggests that the consequences of ER stress may be related to mitochondrial fusion.[7] Prx4 in ER may further influence mitochondrial fusion by acting as an antioxidant defense through sulfur-dependent catalysis to reduce hydrogen peroxide to water. Further investigations are expected to reveal the critical role of Prx4 in influencing mitochondrial function within CECs, which is essential for uncovering new mechanisms to preserve BBB integrity. Besides stroke, Prx4 holds therapeutic potential in the treatment of neurodegenerative diseases. High concentrations of glutamate, which plays a crucial role in the pathogenesis of Alzheimer's and Parkinson's diseases, induce neurotoxicity by triggering the generation of reactive oxygen species (ROS) and causing intracellular Ca^{2+} influx. Research has shown that overexpression of Prx4 mitigates glutamate-induced neuronal apoptosis by inhibiting ROS formation, reducing Ca^{2+} influx, and alleviating ER stress.

Prx4 not only safeguards against early alterations in the CECs but also alleviates subacute brain inflammation (1–3 days post-stroke) through two primary mechanisms: it nullifies proinflammatory reactions within the cerebral vasculature and curtails the incursion of peripheral immune cells.[3] Initially, within 24 hours post-stroke, Prx4 diminishes inflammation along the endothelial lining of brain vasculature. The inflammation of the microvascular walls and the localized generation of proinflammatory cytokines can lead to secondary, and potentially lasting, BBB disruption.

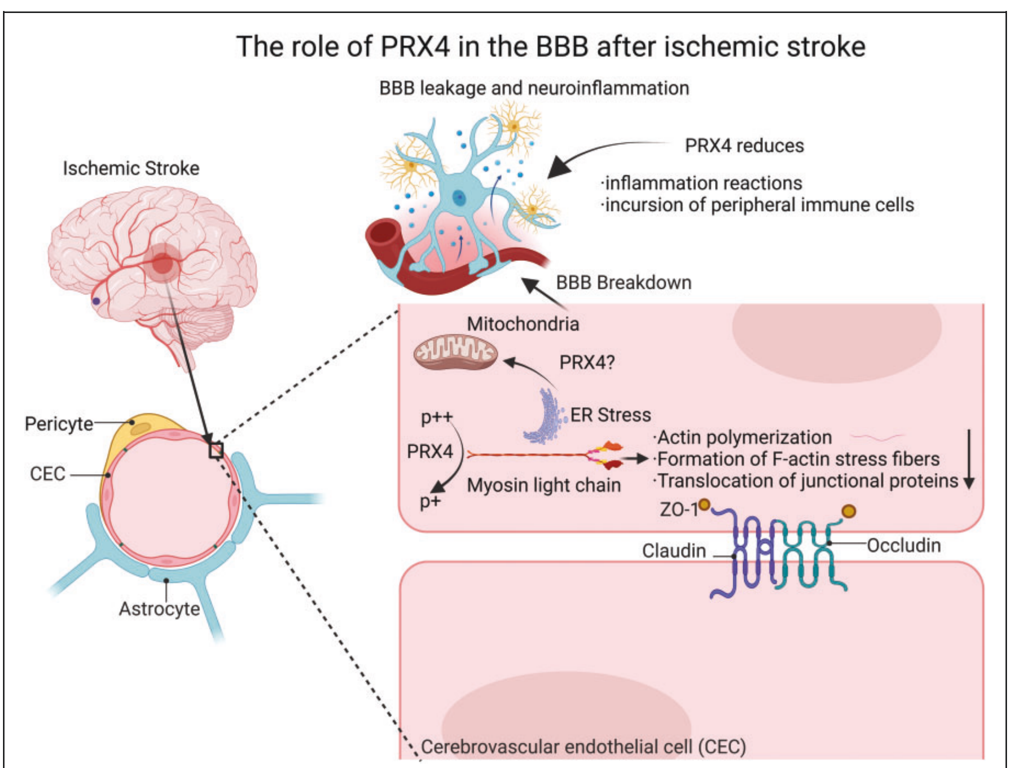

Figure 1. The summary illustrates the critical pathways and molecular mechanisms through which Prx4 contributes to neuroprotection in the context of ischemic stroke, highlighting its impact on reducing inflammation, preserving the integrity of the blood-brain barrier, and mitigating neuronal damage.

Furthermore, acute BBB damage after stroke eases the infiltration of peripheral leukocytes, intensifying secondary brain damage. Prx4 overexpression in ECs reduces this infiltration, particularly of neutrophils and proinflammatory macrophages, thereby diminishing the brain inflammatory load 3–5 days after stroke. Given that neutrophils and macrophages invading from the bloodstream are the main source of brain matrix metalloproteinase (MMP)-9 during this phase of ischemia/reperfusion[8], the prevention of MMP-mediated permanent BBB damage interrupts a harmful, self-perpetuating injury cycle. Collectively, these findings reveal the pivotal role of endothelial Prx4 expression for its substantial impact on long-term stroke recovery. It is also worth noting that in mouse wound healing models, overexpression of Prx4 enhances angiogenesis and improves skin healing.[9] Given the crucial role of Prx4 in ECs, investigating its impact on brain angiogenesis during the chronic injury phase post-stroke is an important area for future research.

The findings from Xu et al. carry significant translational promise for developing a viable stroke therapy. Given that ECs form the initial barrier that systemic therapies encounter, cell-penetrating delivery techniques could efficiently transport this potent protective protein to the site of vascular injury. For instance, this research team has previously utilized a TAT cell-penetrating transduction domain to deliver heat shock protein 27, a protein known to fortify EC structures against ischemia/reperfusion-induced aberrations.[10] Being able to effectively elevate the content of its cargo in ECs,[10] the TAT protein transduction domain offers a feasible strategy for introducing membrane-permeable, recombinant Prx4 protein into these cells. This method holds potential translational value and, if successful, could provide a new avenue for stroke treatment, especially when used alongside recanalization therapies.

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