Endothelial caveolin at the crossroad of thrombo-inflammation coupling

Ayman ElAli

*Neuroscience Axis, Research Center of CHU de Québec - Université Laval, Quebec City, QC, Canada
bDepartment of Psychiatry and Neuroscience, Faculty of Medicine, Université Laval, Quebec City, QC, Canada

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Ischemic stroke constitutes a leading cause of death and disability of the adults. Interruption of the blood supply caused by a thrombus or emboli leads to ischemia followed by reperfusion, which jointly generate an infarct core surrounded by a salvageable penumbra.1 Non-vascular and vascular cells as well as extracellular matrix (ECM) proteins work in concert to generate critical neurovascular functions, such as regulation of blood brain barrier (BBB), cerebral blood flow (CBF), vascular stability, and inflammation.2 Currently, recanalization is achieved through thrombolysis using tissue plasminogen activator (tPA) or endovascular thrombectomy (EVT).3 Nonetheless, the restrictive eligibility criteria of these standard gold interventions limit their broad clinical use. Furthermore, despite successful recanalization, infarct could still progress due to neurovascular deregulation associated with reperfusion-mediated injury. Evidence is suggesting that the crosstalk between thromboembolism and inflammation represents a major culprit in stroke progression.4 Elucidating the mechanisms underlying this pathological crosstalk would allow achieving breakthroughs in stroke therapies through new interventions that aim at attenuating neurovascular deregulation.

Upon endothelial injury, thromboembolism is initiated following exposure of ECM proteins, such as fibronectin and collagen, allowing the activation, adhesion, and aggregation of platelets. Platelet receptor glycoprotein (GP)Ib interaction with von Willebrand factor (vWF) reduces platelet velocity at the injured microvasculature and promotes their interaction with collagen via immunoglobulin superfamily receptor GPVI.5 The release of agonists further enhances the activation and recruitment of additional platelets. The subsequent increased expression of integrin adhesion receptors stabilizes platelet adhesion and facilitates their aggregation by binding fibrinogen.6 Platelets are potently activated and dynamically interacting with the injured distal microvasculature during reperfusion after stroke,7 suggesting that the basic mechanisms of thromboembolism may occur in the distal microvascular bed. However, administration of platelet inhibitors after stroke exhibited modest clinical benefits.8 Furthermore, blockade of platelet aggregation by targeting GPIIb/IIIa was either inefficient or aggravated brain damage due to hemorrhages.6 Interestingly, vWF elevated levels in plasma and GPVI elevated expression in platelets are associated with an increased stroke risk in humans, while experimental attenuation of platelet activation by targeting GPIIb-vWF/GPVI-collagen pathways, was protective.9 These observations suggest that platelet activation, rather than aggregation, constitutes the main pathological process involved in reperfusion-mediated stroke progression.

The pathological events proceeding platelet activation differ between the occlusion of large arteries and deregulation of distal brain microvasculature affected by reperfusion after stroke.7 In the latter, activated platelets pro-inflammatory action mediated by GPIb and GPVI contributes to the deregulation of distal microvasculature located in the penumbra, which compromises tissue salvage, without necessarily leading to re-occlusion with a new thrombus or emboli.7 Nonetheless, the crosstalk between platelet activation and inflammation is still to be elucidated. Evidence is indicating that activated platelets promote immune cell recruitment to the affected microvasculature through a process implicating complex multidirectional interactions with the injured endothelial cells, referred to as “thrombo-inflammation”. Indeed, live imaging experiments confirmed that the excessive adhesion of neutrophils in the injured microvasculature cause vascular stalling that impairs blood perfusion despite efficient recanalization.10 Recent evidence suggests that T cells contribute as well to thrombo-inflammation.11 Although the underlying mechanisms remains to be characterized, activated platelets may guide immune cell recruitment by increasing the expression of adhesion molecules in injured endothelial cells.7

In a recent issue of *eBioMedicine*, Zhang and colleagues described a previously unknown role of
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endothelial caveolin-1 (Cav-1) in regulating thrombo-inflammation after stroke. The authors found that low Cav-1 serum levels correlated with poor prognosis in acute ischemic stroke patients who received EVT. Using a mouse model of ischemic stroke, they reported a down-regulation of Cav-1 in injured endothelial cells following ischemia/reperfusion injury associated with reduced levels in blood circulation. Cav-1 depletion accelerated injury progression by impairing microvascular integrity and upregulating the expression of vWF, plasminogen activator inhibitor (PAI)-I, as well as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecular (VCAM)-1. These changes were associated with an increased recruitment and infiltration of neutrophils and monocytes into the injury site. Notably, rescuing endothelial Cav-1 expression attenuated these detrimental effects. Cav-1-mediated effects were dependent upon retinoid X receptor (RXR)-γ expression in injured brain endothelial cells. RXRs belong to a family of transcription factors that play a central role in maintaining vascular homeostasis. The authors found that RXR-γ repressed ICAM-1 and VCAM-1 expression and limited leukocyte recruitment and infiltration into the injury site. RXR-γ downregulation increased vWF and PAI-1 expression in injured endothelial cells and enhanced fibrinogen aggregation with platelets, outlining RXR-γ’s anti-thromboembolic action.

The reported findings suggest that Cav-1/RXR-γ axis constitutes a main modulator of thrombo-inflammation after stroke. The axis could then be explored to identify novel biomarkers for acute stroke prognosis based on thrombo-inflammation occurrence, and to develop novel therapeutic interventions aiming to fine-tune this process to attenuate stroke progression. To sum up, Zhang and colleagues provided novel mechanistic insights into thrombo-inflammation after stroke, nonetheless more research is urgently required in this important field to improve our current knowledge and to provide new directions in stroke management.

Contributors
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Declaration of interests
The authors declare no conflict of interest.

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