Review Article

Therapeutically Targeting Platelet-Derived Growth Factor-Mediated Signaling Underlying the Pathogenesis of Subarachnoid Hemorrhage-Related Vasospasm

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Introduction: Vasospasm accounts for a large fraction of the morbidity and mortality burden in patients sustaining subarachnoid hemorrhage (SAH). Platelet-derived growth factor (PDGF)-β levels rise following SAH and correlate with incidence and severity of vasospasm. *Methods:* The literature was reviewed for studies investigating the role of PDGF in the pathogenesis of SAH-related vasospasm and efficacy of pharmacological interventions targeting the PDGF pathway in ameliorating the same and improving clinical outcomes. *Results:* Release of blood under high pressure into the subarachnoid space activates the complement cascade, which results in release of PDGF. Abluminal contact of blood with cerebral vessels increases their contractile response to PDGF-β and thrombin, with the latter upregulating PDGF-β receptors and augmenting effects of PDGF-β. PDGF-β figures prominently in the early and late phases of post-SAH vasospasm. PDGF-β binding to the PDGF receptor-β results in receptor tyrosine kinase domain activation and consequent stimulation of intracellular signaling pathways, including p38 mitogen-activated protein kinase, phosphatidylinositol-3-kinase, Rho-associated protein kinase, and extracellular regulated kinase 1 and 2. Consequent increases in intracellular calcium and increased expression of genes mediating cellular growth and proliferation mediate PDGF-induced augmentation of vascular smooth muscle cell contractility, hypertrophy, and proliferation. *Conclusion:* Treatments with statins, serine protease inhibitors, and small molecular pathway inhibitors have demonstrated varying degrees of efficacy in prevention of cerebral vasospasm, which is improved with earlier institution. **Key Words:** Vasospasm—subarachnoid hemorrhage—platelet-derived growth factor—statins—complement—nafamostat mesylate—ROCK—MAPK.

Introduction

Subarachnoid hemorrhage (SAH) is a major cause of neurologic morbidity and mortality. Cerebral vasospasm and delayed cerebral ischemia (DCI) are second only to the initial hemorrhage and rebleeding as causes of underlying poor outcome in patients with aneurysmal SAH.[1] Studies have revealed a multifactorial and complex pathogenesis for the development of vasospasm, with vasoconstriction and vascular smooth muscle cell (VSMC) hyperplasia or hypertrophy appearing to play important and therapeutically interventionable roles.[2-14]

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Over the past 3 decades, there has been a gradual evolution in conceptualization of the mechanism underlying SAH-related vasospasm. Oxyhemoglobin was initially posited as a principal mediator underlying vasospasm.[15-18] However, oxyhemoglobin was shown not to precipitate significant vasoconstriction in rabbit basilar artery[19] and its levels exhibited an unexpected inverse relationship to magnitude of basilar vasospasm following SAH in dogs.[20]

In the mid-1990s through 2000s, endothelin came to the forefront as a chief culprit in the etiopathogenesis of vasospasm.[21] Supporting this, blockade of endothelin receptors demonstrated efficacy in phase II randomized control trials (RCTs) in attenuating radiographic vasospasm.[21-25] However, there was no benefit by clinical metrics in a large randomized prospective cohort (n = 1157).[26] This led to growing appreciation for, and an integration of, long-acting growth factor-mediated mechanisms in the conceptual framework for vasospasm pathogenesis,[16,17,27-31] with a principal candidate being platelet-derived growth factor (PDGF)-β.[32-36]

Growing evidence supports an increasingly critical role for PDGF-β in mediating SAH-related vasospasm. PDGF-β contributes both to the early vasoconstrictive phase of vasospasm, via increased VSMC contractility and promotion of neutrophil chemotaxis and the late vascular remodeling phase of vasospasm, via promotion of VSMC hyperplasia and hypertrophy. Thus, targeting upstream regulators and downstream mediators of PDGF-mediated signaling may hold therapeutic promise for reducing the incidence and severity of vasospasm.

PDGF in the Pathogenesis of Vasospasm

Regulation of PDGF

PDGF is a cellular growth and division-promoting polypeptide consisting of homo- or heterodimers of alpha and beta chains synthesized and released by endothelial cells, macrophages, and platelets.[37] Hypoxia, ischemia, inflammatory mediators, and direct contact with thrombin all increase the expression of PDGF, which can further enhance its own production.[35,38,39] PDGF receptors (PDGFRs) are found principally in vascular tissue (e.g., VSMCs), immune and repair cells (e.g., monocyte, fibroblasts), and the central nervous system (e.g., neurons, glia).[35,40-44]

PDGF Levels Rise Following SAH and Predict Incidence and Severity of Vasospasm

PDGF levels rise in both serum and cerebrospinal fluid (CSF) following SAH in both animal models and human patients.[45-49] This PDGF derives primarily from platelets and macrophages and its rise occurs as early as 3 hours post-SAH in rabbit models.[49] In early SAH, PDGF expression localizes principally to VSMCs (and endothelial cells to a lesser extent) exhibiting a temporal profile mirroring that of maximal vasospasm risk. Importantly, degree of vessel stenosis directly correlates with temporal expression dynamics of PDGF-β, as demonstrated in a rabbit model of SAH.[49] In human patients with SAH, higher PDGF levels predict greater probability of developing cerebral vasospasm and DCI,[46-48] with individuals developing DCI exhibiting higher PDGF CSF levels (3.9 ng/mL) compared to their unaffected counterparts (1.1 ng/mL).[46]

PDGF as an Intermediary between Abluminal Contact with Subarachnoid Blood and Vasospasm

Although reflecting an attempt at a repair response to injury[48] and conferring resistance of the brain to hypoxia,[50,51] increased PDGF following SAH mediates principally deleterious effects, with strong evidence supporting a causative role in SAH-related vasospasm. Intrasubarachnoid instillation of PDGF-β was shown to cause cerebral vasospasm, recapitulating the effects of subarachnoid blood, an effect blocked by inhibitors of PDGFR synthesis and signaling pathways downstream from PDGF-β (e.g., trapidil, fasudil).[52,53] Thrombus-adjacent elevation of PDGF-AB along with concurrent VSMC hyperplasia following SAH are blunted following treatment with neutralizing antibodies targeting PDGFs.[54] The alpha chain of PDGF, however, does not appear to induce a contractile response in VSMCs.[52]

Blood in contact with the abluminal surface of cerebral vessels has been shown to promote the contractile response to PDGF[35] and thrombin.[55] Thrombin-induced upregulation of PDGFR-β also contributes to the former effect.[35] The presence of ventricular blood greatly elevates the risk of developing cerebral vasospasm and consequent DCI,[56,57] presumably a consequence of slow diffuse release of PDGF-β into the CSF.

Beyond the simple presence of blood in the subarachnoid space and ventricular system, the pressure under which blood is released into the subarachnoid space appears critical in risk for developing vasospasm, as PDGF-β synthesis has been shown to increase in direct proportion to the degree of arterial stretch.[58] This explains high rates of vasospasm following aneurysmal SAH and absence of the same in benign perimesencephalic SAH, which results from rupture of low pressure anterior pontomesencephalic veins.[59] Volume of blood on initial head computed tomography thus predicts the incidence and severity of vasospasm, in part, as a consequence of an initial higher velocity of transluminal blood egress into the subarachnoid space and consequent greater rapidity of arterial stretch following aneurysmal SAH.

Molecular Pathways Mediating PDGF-Induced Vasospasm

Platelet, macrophage, and endothelial cell release of PDGF-β following SAH is initiated by, and requires, the activity of functional complement protein factors. The release of blood into the subarachnoid space under high pressure results in (1) activation of complement, which