In this issue of PNAS, Wei and colleagues demonstrate that the Nuclear factor erythroid 2-related factor 2 (Nrf2), a well-known cell-intrinsic cytoprotective factor and critical regulator of the anti-oxidant response plays an important function in reparative angiogenesis by suppressing the antiangiogenic effects of Semaphorin 6A (Sema6A), a membrane-associated guidance molecule expressed by neurons during retinal ischemia (1).

Ischemic vasoproliferative retinopathies such as diabetic retinopathy, retinal vein occlusion and retinopathy of prematurity are considered some of the main causes of visual impairment and blindness in adults and children respectively. These ocular diseases are characterized by a retinal microvascular degeneration followed by an abnormal intravitreal neovascularization. One of the major concerns about ischemic retinopathies is to understand the mechanism by which retinal revascularization proceeds aberrantly towards the vitreous instead of within the inner limiting membrane. Recently, it has been hypothesized that some forms of repulsive factors interfered with normal revascularization of the vaso-obliterated regions of the retina, and as a result led to misguidance of vessels towards the vitreous (2,3). However, none of these repulsive factors was associated before to key regulatory molecules such as Nrf2 that has the potential to reprogram ischemic tissue toward a neurovascular repair response.

Oxidative stress is considered a significant trigger of the tissue damage in ischemic retinopathies (4). Nrf2 is an important suppressor of the oxidative damage in the tissues and therefore it has become a key player in the protection against retinal diseases. It has been reported that the absence of functional Nrf2 in the retina reduces the ability to respond to oxidative stress and accelerate degenerative changes in a model of ischemic retinopathy (5). In a previous study, Wei et al. proposed that the Nrf2 activation during developmental angiogenesis in the retina has a proangiogenic effect (6). However, its role in ischemic vasoproliferative retinopathies remained poorly understood. Herein, by using the mouse model of oxygen-induced retinopathy (OIR), a well characterized model that mimics the two phases that occur in ischemic retinopathies in humans, Wei and colleagues showed that Nrf2 can regulate revascularization of the neuroretina after ischemia by coordinating neuronal and endothelial elements. To demonstrate the reparative angiogenic mechanism of Nrf2 in OIR, Wei and colleagues focus their attention particularly in the site of vaso-obliteration and reparative angiogenesis in OIR. The authors found a major expression and nuclear localization of Nrf2 (activation) in retinal ganglion cells located in the avascular retina associated to the reparative angiogenesis. Conversely, genetic ablation of Nrf2 dramatically impeded vascular regeneration and increased pathological neovascularization in the retinas of animals subjected to OIR. Importantly, the absence of Nrf2 was accompanied by an increased expression of the antiangiogenic/repulsive factor Sema6A in the ganglion cell neurons from ischemic inner retina in OIR mice. These results, along with other studies (2,3) further support the evidences that neuron repulsive cues increase in the ischemic retina of OIR animals inhibits vascular regeneration and/or promotes pathological neovascularization. Distinctively, in this study no appreciable changes on other repulsive cues were detected suggesting that the suppression of vascular regrowth in the absence of Nrf2 is specifically attributed to
the neuronal repulsive factor Sema6A, which has also been shown to exert antiangiogenic activity in other models (7,8), but never proven to be regulated by Nrf2. The regulation of Sema6A by Nrf2 in hypoxic stress-injured neurons was HIF-1α-dependent, which is not surprising, since HIF-1 is part of the primary cellular response to hypoxia and can activate a range of genes involved in several cellular processes.

Impaired ischemic neurovascular remodeling by expressing neuronal guidance cues, such as Sema3A, Sema3E and Sema6A, uncovers an important mechanism that involves the semaphorins in the inhibition of the reparative angiogenesis into the hypoxic/ischemic zone in vasoproliferative retinopathies. Interestingly, and in contrast to other secreted semaphorins, Sema6A has been shown to be a membrane-associated guidance molecule that suggests its vasorepulsive effect by direct contact between endothelial cells and retinal ganglion cells.

To emphasize the hypothesis that Sema6A mediates the suppression of revascularization in the retina in vivo, the investigators tested the effects of extracellular Sema6A on endothelial cell motility. They found that Sema6A induced cellular contraction, inhibited cell migration and decreased tube formation on endothelial cell cultures in a dose-dependent fashion. Importantly, Sema6A suppresses migration via activation of Notch signaling, a well-characterized mechanism implicated in the regulation of angiogenesis.

Given the antiangiogenic and vasorepulsive properties of Sema6A, it was logic for the authors to propose that local inhibition of Sema6A would limit the invasion of the pathologic new vessels toward the vitreous. This hypothesis was confirmed when the intravitreal administration of lentivirus containing small hairpin RNA (shRNA) targeting Sema6A significantly reduced avascular area and inhibited pathologic preretinal neovascularization in the absence or presence of Nrf2 in animals subjected to the OIR model. This result raises the possibility of Sema6A inhibition as a therapy for pathologic retinal neovascularization. Also given the important role of Nrf2 in the reparative angiogenesis during OIR, the authors suggest that pharmacological enhancement of Nrf2 could be a novel therapeutic strategy for this condition. To prove this, Wei and collaborators performed intravitreal injections of synthetic triterpenoids, which are potent inducers of Nrf2, and as they expected, an increase in vascular regeneration as well as a suppression of preretinal neovascularization it was detected in OIR animals. These findings strongly suggested Nrf2 as a therapeutic target in diseases related to ischemia-induced angiogenesis in the retina and the central nervous system.

The study by Wei and colleagues represents a significant contribution to the mechanisms implicated in development of ischemic retinopathies. This elegant study highlights the critical role played by neurons and endothelial cells in governing vascular repair. The mechanism provided by the investigators addresses a framework for understanding how the presence of vasorepulsive factors in the avascular and severely hypoxic retina form a chemical barrier preventing vascular ingrowth into the ischemic zone. This study also provides a novel link between Nrf2 and Sema6A. The observation that Nrf2 can regulate local Sema6A expression serves as a guide for future studies regarding the possible role of Nrf2 in modulating other semaphorins or factors implicated in different pathologic conditions such as stroke or cancer. The fact that Nrf2 and Sema6A participate as regulators of the neuroretinal response to ischemia suggests a therapeutic strategy directed at shifting the neuroretina toward a repair response, specifically by promoting revascularization. This might involve enhancing Nrf2 activation to influence the overall neurovascular response, or suppressing Sema6A and its critical antiangiogenic effect. Finally, the work by Wei et al., provides a valuable conceptual framework with fruitful avenues for future investigations and a blueprint to understand the pathogenesis of other ischemic disorders.

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Footnote

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References


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