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The role of vascular endothelial cadherin and the therapeutic potential of intravitreally administrated mesenchymal stem cells in retinal vasoregression

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Pericytes and endothelial cells are the major players in maintaining retinal neurovascular unit (NVU) integrity. Pericytes contribute to vascular protection and regeneration in the retina. Previous studies reported that pericyte loss has been detected in several animal models of retinopathy with the breakdown of NVU, such as NDPK B-/- mice (5-month old), PKD rats (2-month old), and Ins2Akita mice (3-month old). VE-cadherin is exclusively expressed in endothelial cells and preserves the endothelial barrier functions. Reduced expression of VE-cadherin leads to increased vascular permeability. However, the correlation of altered VE-cadherin and pericyte loss, and the underlying mechanism are still not fully elucidated. From the therapeutic perspective, pericytes have been a therapeutic target in diseases with retinal vascular degeneration. Mesenchymal stem cells (MSCs) and pericytes share typical cell morphology and phenotypic characteristics. Thus, MSC-based therapy has been proposed as an alternative therapeutic approach in retinal degenerative diseases. Therefore, the study aims to identify: 1) the link between retinal VE-cadherin expression and pericyte loss in animal models with vasoregressive retinopathy, and the underlying signal transduction, 2) the therapeutic potential of intravitreally administrated MSCs in retinopathy with vasoregression.
The study showed that:
1. Reduced VE-cadherin was found in the retinas of 4-month-old NDPK B-/- mice, 1.5-month-old Ins2Akita mice, and 1-month-old PKD rats prior to pericyte loss.
2. In NDPK B-/- mice, retinal vascular permeability was increased. Reduced VE-cadherin expression was predominantly detected in the deep retinal capillary layer.
3. In vitro, either NDPK B deficiency or high glucose lowered VE-cadherin in the endothelial plasma membrane by promoting Src kinase activation followed by VE-cadherin tyrosine phosphorylation (Y685), leading to internalization and degradation in a lysosome-dependent manner. Moreover, reduced expression of VE-cadherin in endothelial cells led to pericyte loss.
4. Intravitreal administration of MSCs in both SD and PKD eyes induced or aggravated cataract, pericyte loss, and formation of acellular capillaries.
5. MSCs remained in the vitreous cavity and did not migrate into the retinas.
6. Intravitreal administration of MSCs impacted retinal neuronal function neither in SD nor PKD rats.
7. Intravitreal injection of MSCs activated retinal micro- and microglial cells in SD rats.
8. Intravitreal injection of MSCs increased the expression of inflammatory factors (IL-1β, C3, and Arg1) and enhanced HSP90 expression in SD rats.
In conclusion, our data suggest that the alteration of retinal VE-cadherin precedes pericyte loss independent of hyperglycemia in different experimental animal models with early retinopathy. VE-cadherin reduction induces pericyte loss through Src kinase activation and increased VE-cadherin Y685 phosphorylation. We identify a novel signaling pathway involved in VE-cadherin-mediated pericyte loss. It provides new insight into the therapeutic intervention of retinopathy with NVU breakdown. However, the destructive effect of MSCs in the eyes indicates that intravitreal administration of MSCs is inadvisable.