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The role of VE-cadherin Tyr 685 in the breakdown of the neurovascular unit in experimental diabetic retinopathy

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Diabetic retinopathy is one of the most common complications associated with diabetes mellitus, marked by the progressive dysfunction of retinal blood vessels and nerve cells. Vascular endothelial cadherin, an essential element of the adherens junctions, is crucial for maintaining the integrity of blood vessels. The phosphorylation of vascular endothelial cadherin at tyrosine position 685 has been linked to the regulation of vascular permeability, yet its specific function in diabetic retinopathy remains poorly understood.

Using a mouse model with a mutation that hinders phosphorylation at tyrosine 685, we investigated the effects on retinal vascular and neural injury in diabetic retinopathy and pre-diabetic retinopathy. Our findings demonstrate that the tyrosine 685 mutation protects against diabetic retinal damage including vascular hyperpermeability, pericytes loss, and acellular capillary formation. Additionally, this mutation suppressed the activation of the hexosamine biosynthesis pathway and upregulation of angiopoietin 2, both of which are crucial in the vascular impairment in diabetic retinopathy. In an animal model of pre-diabetic retinopathy, the nucleoside diphosphate kinase B deficient mouse, the tyrosine 685 mutation similarly mitigated vascular damage by reversing the activation of the hexosamine biosynthesis pathway and the upregulation of angiopoietin 2, indicating a protective mechanism that operates independently of hyperglycemia. Furthermore, this mutation preserved retinal neuronal function, as evidenced by multifocal electroretinography, and suppressed Müller cell activation, a key feature of glial reactivity in diabetic retinopathy.

The findings underscore the crucial role of vascular endothelial cadherin phosphorylation at tyrosine 685 in the development of diabetic and pre-diabetic retinopathies. Targeting this phosphorylation site offers a promising therapeutic strategy for vascular and neural dysfunction in diabetic and pre-diabetic retinopathies. This research provides valuable insights into mechanisms underlying retinal damage and highlights the potential of vascular endothelial cadherin phosphorylation in treating diabetic complications.