Vessel Remodeling in Diabetic Retinopathy

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Background

Several mechanisms have been proposed to account for hyperglycemia-induced vasculopathy. While Notch signaling was reported to be affected by glucose metabolism in endothelial cells during developmental angiogenesis, it has not been investigated in vascular remodeling of adult capillaries in relation to hyperglycemia.

Methods and Results

We show that hyperglycemia induces retinal microvasculopathy (RM), characterized by capillary remodeling, regression, or decreased density, in adult mice with streptozotocin-induced hyperglycemia. Immunofluorescence and confocal microscopy revealed that Notch ligand Jagged1, but not Dll4, was markedly increased in the retinal endothelial cells of hyperglycemic mice. Using endothelial specific-Jagged1 knockdown mice, we found that blocking Jagged1 prevented RM even under hyperglycemic conditions. Furthermore, using the inducible endothelium-specific Jagged1-knockdown mice, blocking Jagged1 even at 4 weeks after establishment of RM could reverse it, leading to normalization of retinal vasculature. A search for downstream signals revealed that hyperglycemia decreased the nuclear localization of NICD1 (Notch1 Intracellular Domain) in endothelial cells. Chemical Notch inhibition phenocopied RM in normal mice.

Conclusions

Taken together, our findings indicate that hyperglycemia induces Jagged1 overexpression and suppresses Notch signaling in endothelial cells, leading to RM in adult mice. We conclude that dysregulated intercellular Notch signaling may be a novel mechanism of diabetic microvasculopathy.