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Association between Increased Vascular Density and Loss of Protective RAS in Early-Stage NPDR

Purpose.

Our hypothesis predicts that retinal blood vessels increase in density during early-stage progression to moderate nonproliferative diabetic retinopathy (NPDR). The renin-angiotensin system (RAS) is implicated in the pathogenesis of DR and in the function of circulating angiogenic cells (CACs), a critical bone marrow-derived population that is instrumental in vascular repair.

Methods.

Arterial and venous patterns extracted from images of 6 normal controls and 3 early NPDR subjects (2 moderate, 1 mild) by Spectralis® OCT following fluorescein angiography (FA) were mapped by NASA's VESsel GENeration Analysis (VESGEN) software to yield branching generations (G_x) quantified by parameters that include densities of vessel length (L_v), area (A_v) and number (N_v). Peripheral blood of diabetics and controls was collected for $CD34^+$ CAC isolation. RAS gene expressions in CACs were measured by qPCR for Mas receptor for Ang-(1-7). Vasoreparative function of CACs was assessed by migration ability toward CXCL12 (SDF-1) using QCM 5μM 96-well chemotaxis cell migration assay.

Results.

By VESGEN analysis, vessel density measured by L_v, A_v, and N_v in early NPDR was greater than in control. For example, L_v was 2.00±0.06E-2 px/px^2 in NPDR veins for all branching generations compared to 1.01±0.06E-2 px/px^2 in control, and 1.64±0.13E-2 px/px^2 compared to 8.90±1.37E-3 px/px^2 in arteries. Results were confirmed by other parameters such as A_v and N_v. The expression of Mas in CACs was reduced in NPDR relative to control, indicating possible loss of compensation of the protective RAS at this stage of DR. NPDR was associated with $CD34^+$ CAC migratory dysfunction toward CXCL12, which was corrected with Ang-(1-7) pretreatment prior to CXCL12 exposure.

Conclusions.

For our ongoing longitudinal study, preliminary evidence by VESGEN indicates that vascular density increased in early NPDR compared to control. If confirmed by more complete analysis, results are potentially of value for determining optimal therapies at early stages of NPDR, when regenerative vascular treatments are more likely to be successful. These data also suggest the protective RAS axis within diabetic CACs is lost early in DR and is associated with increased vascular remodeling evidenced by VESGEN analysis.

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