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HIGH GLUCOSE CONDITION INDUCED JAGGED-1 OVEREXPRESSION AND NOTCH INHIBITION, RESULTING IN THE ABERRANT ENDOTHELIAL TUBE FORMATION: A NOVEL MECHANISM OF DIABETIC MICROVASCULOPATHY IN A MODEL OF HUMAN ANGIOGENESIS

Poster Contributions
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Background: Endothelial intercellular signaling related to diabetic vasculopathy has not yet been validated due to lack of a proper model to study. We developed an in vitro model of human angiogenesis to identify a pathologic intercellular signaling in high glucose condition.

Methods: We co-cultivated human endothelial cells (hEC) and human smooth muscle cells (hSMC) in spheroid on hSMC monolayer for 7 days. We cultured this hybrid (EC and SMC) spheroid in 25.6mM glucose medium for high glucose condition whereas in 5.6mM for normal. We visualized and compared vascular growth with confocal microscopy and time-lapse fluorescent microscopy.

Results: We could observe multi-step process of human angiogenesis using in vitro hybrid spheroid model, including sprouting tip cells and tube-forming stalk cells, lumenization, and vascular network formation. We could recapitulate abnormal angiogenesis by modulating notch signaling as in the mouse model of postnatal retina angiogenesis. Both inhibition of notch1 with γ-secretase inhibitor and overexpression of jagged-1 induced abnormal angiogenesis that was characterized by the increased sprouting and branching points, the decreased vascular diameter and length, and destabilization of the tubes. Such an abnormal angiogenesis was also observable in the high glucose condition (high glucose vs. normal: number of sprouts 20.3±1.5 vs 13.7±2.9, p=0.024; number of branching points 7.6±2.5 vs 2.3±2.1, p=0.047; diameter of the tubes 13.4±6.1μm 19.1±8.8μm, p=0.012). As the underlying mechanism of high glucose-induced aberrant angiogenesis, we identified the PKC- and NF-kB-dependent upregulation of jagged1 in hEC exposed to high glucose. Thus, shRNA targeting jagged1 could rescue the aberrant angiogenesis in high glucose condition.

Conclusions: We found that abnormal endothelial notch signaling might be a mechanism of diabetic microvasculopathy. Correction of the pathologic angiogenesis by modulating the aberrant signaling in the present study highlighted a future direction of treatment of diabetic vasculopathy beyond glucose control.