A Predictive, Mechanism Based, Multicell Model of Pathological Vascularization in the Retina

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The hallmark of *wet* or *exudative* age-related macular degeneration (*AMD*), a leading cause of irreversible blindness, is the invasion of the retina by new blood vessels growing from the choriocapillaris (*CC*) (choroidal neovascularization, *CNV*). In humans, CNV frequency increases with age, and numerous risk factors and insults can increase its probability in an individual. The factors controlling CNV initiation and progression are poorly understood. Two current treatments for CNV either kill the invading blood vessels with drugs injected into the eye (also damaging the retina and killing needed blood vessels as well) or laser ablate the blood vessels, which can cause damaging retinal scars. Neither treatment addresses the underlying problems that caused the blood vessels to invade, so relapses are common and many patients lose vision within a year or two of treatment. We have developed a computational model that allows us to investigate the effects of specific mechanisms and study the synergism/antagonism of multiple mechanisms acting simultaneously. Our 3D multi-cell model includes key retinal components, mechanisms (including cell-cell, cell-extracellular matrix (ECM) and ECM-ECM adhesion), and angiogenesis-related processes. For example, we include Bruch's membrane (BrM) breakdown, hypoxic signaling and upregulation of vascular endothelial growth factor (VEGF), and VEGF and oxygen transport.

We used our model to simulate a wide range of age-related defects and perturbations in the retina and explore their role in CNV initiation and progression: 1) VEGF overexpression in the retinal pigment epithelium (RPE), 2) defects in BrM, and 3) Defects in adhesion in CC-BrM-RPE complex. From a large ensemble of simulations of these defects, we have computed multi-dimensional risk maps showing the significance of both single perturbations and combinatory perturbations.

Our key findings are: 1) Sub-RPE CNV only forms when attachment of the basement membrane of the RPE to BrM fails. 2) VEGF overexpression increases risk of initiating sub-retinal CNV, but it does not promote sub-RPE CNV. 3) Holes in BrM larger than about 40 μm disrupt RPE integrity leading to sub-retinal CNV, but not sub-RPE CNV. Our computational results agree with clinical and experimental observations and provide a mechanistic explanation.

Our CNV risk maps make clinically-useful suggestions for frequency of follow-up and possible prophylactic interventions based on clinically-measurable properties of the eye.