James Glazier
Indiana University
e-mail: glazier@indiana.edu
Abbas Shirinifard
Indiana University

Multi-scale, Multi-cell Computational Modeling of Choroidal Neovascularization in Age-Related Macular Degeneration

Choroidal neovascularization (CNV) of the macular area of the retina is the major cause of severe vision loss in patients with age-related macular degeneration (AMD) and the major cause of vision loss in adults in the developed world. In CNV, after choriocapillaries initially penetrate Bruch's Membrane (BrM), the invading vessels may regress or expand (CNV initiation). After initiation, during early and late CNV, the expanding vasculature usually spreads in one of three distinct patterns: in a layer between BrM and the retinal pigment epithelium (sub-RPE, occult or Type 1 CNV), in a layer between the RPE and the photoreceptors (subretinal, classic or Type 2 CNV) or in both loci simultaneously (combined pattern or Type 3 CNV). The factors determining both CNV initiation and progression are poorly understood. While most previous studies of CNV have assumed that it is primarily related to growth factor effects or to local holes in BrM, our simulations of a three-dimensional (3D) multi-cell model of the maculae of normal and pathological retinas successfully recapitulate the three clinically observed types of CNV, under the hypothesis that initiation and early and late CNV result from combinations of impairment of: 1) RPE-RPE epithelial junctions (i.e. the outer blood-retinal barrier), 2) the adhesion of the basement membrane of the RPE (BaM) to BrM, and 3) adhesion of the RPE to the photoreceptor outer segments (POS). Our key findings are that when an endothelial tip cell or immune cell penetrate BrM: 1) RPE with normal epithelial junctions and basal attachment to BrM and apical attachment to POS resists CNV, showing that higher rates of EC activation due to excess vascular growth factors by themselves are insufficient to produce CNV. 2) Similarly small holes in BrM do not, by themselves, initiate CNV. 3) RPE with normal epithelial junctions and normal apical RPE-POS adhesion, but weak adhesion of BaM to BrM (e.g. due to lipid accumulation in BrM) initially results in Type 1 CNV. 4) Normal adhesion of BaM to BrM, but reduced apical RPE-POS and epithelial RPE-RPE binding (e.g. due to inflammation) initially results in Type 2 CNV. 5) Simultaneous reduction in RPE-RPE epithelial binding and BaM-BrM adhesion results in early Type 1 or 2 CNV which often progresses to Type 3 CNV as neovascularization further perturbs RPE-RPE adhesion and BaM-BrM attachment. These findings suggest that previously neglected changes in adhesion rather than the more often hypothesized excess production of vascular growth factors dominate both CNV initiation and progression.