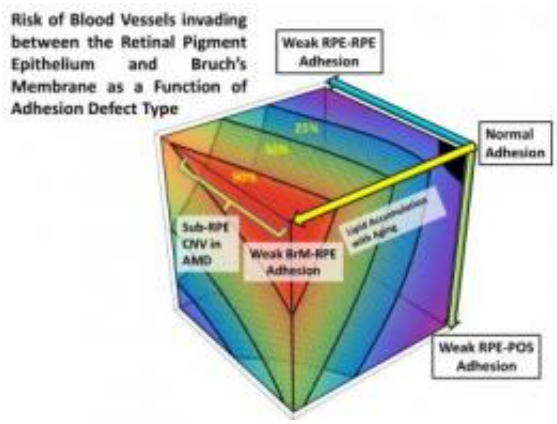
Medical Xpress

Sloppy shipping of human retina leads researchers to discover new treatment path for eye disease

May 4 2012



The black region shows normal adhesion, with each black axis an independent type of adhesion failure. The red region shows adhesion defects making invasion most likely, as the yellow arrow denotes increasing risk of blood vessel invasion in the retinal pigment epithelium (RPE) lining. The blue arrow follows reduced adhesion but with no increased risk of sub-RPE invasion; green arrow shows reduced adhesion between RPE and photoreceptors (POS) from impaired retina, reducing risk of sub-RPE invasion but increasing risk of other types of invasion. Credit: Indiana University Biocomplexity Institute

Sloppy shipping of a donated human retina to an Indiana University researcher studying a leading cause of vision loss has inadvertently helped uncover a previously undetected mechanism causing the disease. The discovery has led researchers to urge review of how millions of

dollars are spent investigating the cause of a type of age-related macular degeneration called choroidal neovascularization.

Working at IU's Biocomplexity Institute, postdoctoral researcher Abbas Shirinifard had hit a brick wall trying to develop detailed computer simulations of the behaviors and interactions of the cells and membranes composing the rear of the retina and its supporting vasculature. In choroidal neovascularization (CNV), blood vessels that supply the eye with oxygen and nutrients and originate in the choroid just behind the eye abruptly break into the retina and disrupt it. Blindness can follow in a matter of months.

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-heat the blood vessels, which can cause damaging retinal scars. Yet with 9,000 research papers published on CNV over the past 10 years, neither treatment still addresses the underlying problems that cause the blood vessels to invade, so relapses are common and many patients still lose vision within a year or two.

A serendipitous accident in which a donated human retina from an eye bank was severely shaken during shipping inspired Shirinifard to try again with a series of new simulations. Upon examination of the eye, Shirinifard and Biocomplexity Institute senior microscopist Sherry Clendenon found that regions of the retina with invading blood vessels had separated from their underlying membrane, while regions that had stayed attached showed much less invasion, suggesting that adhesion might be an essential but overlooked mechanism in maintaining the retina's structure.

Using an open-source modeling software program called CompuCell3D developed by the Biocomplexity Institute in collaboration with the University of Washington and the University of Wisconsin under

National Institutes of Health funding, the team quickly began extending existing simulations to study the effects of adhesion defects.

"The simulations showed that reduced adhesion in the retina could indeed lead to its invasion by blood vessels," Shirinifard said. "But the complex structure of the retina meant that many types of adhesion could be important -- the three most prominent being between the pigmented retinal cells (the black lining of the eye) and Bruch's membrane (the substrate that supports the retina), between adjacent pigmented retinal cells, and between pigmented retinal cells and the overlying photoreceptors."

Those variables, the team realized, could be independent of one another or interact in complex ways, and knowing that the rate and type of progression of the disease varies greatly from patient to patient, they needed to examine many examples of each adhesion combination.

That's when Quarry, the IU computer cluster operated by the Office of the Vice President for Information Technology, was called in to push out 32,000 hours of calculations.

"We were able to model the interactions of different degrees of impairment of each type of adhesion and the variation from case to case," Shirinifard said. "Amazingly, these simulations were able to replicate the complex spectrum of CNV seen in the clinic."

Simulations of adhesion defects caused by reduced adhesion between pigmented retinal cells and Bruch's membrane -- the type of CNV typical of aging -- produced a pattern and frequency of invasion agreeing with that in the clinic. Similarly, reduced adhesion between neighboring pigmented retinal cells, typical of inflammation due to severe infection, produced a pattern of invasion agreeing with that seen in young adults.

By combining thousands of simulations, Shirinifard was able to produce maps that related defects in each type of adhesion to the risk of each type of invasion. In turn, he could show that cell adhesion is key to keeping blood vessels out of the retina and that combination defects in the different types of adhesion are sufficient to determine the probability, pattern and rate of progression of CNV.

The full results of one of the most complex tissue evolution models ever deployed were published today in *PLoS Computational Biology*, and while the team has yet to move toward developing new CNV therapies, the work should have great significance in the search for better therapies, according to Biocomplexity Institute Director James Alexander Glazier, a co-author on the paper and professor in the IU Bloomington College of Arts and Sciences' Department of Physics.

"Hundreds of millions of dollars are spent annually to develop drugs and treatment approaches based on the two commonly hypothesized CNV initiation and progression mechanisms," he said. "Because the current work shows that neither hypothesized mechanism is an important cause of CNV, that money and effort are extremely unlikely to improve outcomes for patients. Scientists have been barking up the wrong tree. Instead, a search for therapies which restore normal adhesion in the eye is much more likely to produce effective treatments. In addition, the detailed agreement between simulation and clinical observations suggests that new approaches to measuring adhesion in patients would allow much more accurate predictions of the prognosis for individual patients."

The researchers believe these results will also have a much broader impact, as they apply to any tissue -- like the gut and the lung -- in which a basement membrane separates a capillary network from a nearby epithelium.

"The relationships between specific classes of adhesion failures and the types and dynamics of CNV in the eye simulations should carry over to the neovascularization-dependent pathologies of those tissues and to invasion of those tissues in cancer progression," Shirinifard said.

Provided by Indiana University

Citation: Sloppy shipping of human retina leads researchers to discover new treatment path for eye disease (2012, May 4) retrieved 2 May 2024 from
https://medicalxpress.com/news/2012-05-sloppy-shipping-human-retina-iu.html