European Journal of Ophthalmology / Vol. 10 no. 1, 2000 / pp. 1-3

Editorial

Interfaces

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There are important similarities in molecular composition and structural organization of the interface between the vitreous and retina and that between the retina and retinal pigment epithelium. It is striking that the two most common causes of severe vision loss in the western world involve neovascularization at these interfaces; i.e., proliferative diabetic vitreoretinopathy at the vitreo-retinal interface and exudative age-related macular degeneration at the retina-retinal pigment epithelium interface. Improved knowledge of the physiology of these interfaces will lead to a better understanding of the effects of aging and diseases, especially those that involve neovascularization. Such advances will no doubt result in new treatment strategies offering more effective therapy, and, even more importantly, perhaps providing prevention from these devastating causes of blindness. (Eur J Ophthalmol 2000; 10: 1-3)

KEY WORDS: *Vitreous, Retina, Interface, Extracellular matrix, Interphotoreceptor matrix, Retinal pigment epithelium, Neovascularization, Bruch's membrane*

Accepted: January 5, 2000

That certain biological phenomena occur in different species, in various organs of a given organism, and even in different tissues within the same organ has long been exploited as a useful principle in biomedical research. The ability to transfer knowledge gained from the study of one species or organ system to another has made possible great strides in advancing our knowledge without incurring unacceptable risks or unbearable costs in conducting valuable research. Study of the molecular composition, structure, and pathobiology of extracelllular matrices is an excellent example of this thesis. In the eye, two critically important extracellular compartments are located at the retina-retinal pigment epithelium-Bruch's membrane interface, and the vitreo-retinal interface. These seemingly disparate interfaces are rendered quite alike by the presence of similar molecular components and comparable structural organization of those components. Not surprisingly, they also share concurrent age or disease-related changes as they have similar responses to physiologic disturbances and pathologies.

At the retina-retinal pigment epithelial interface, the interphotoreceptor matrix is delineated by the apices of Müller, photoreceptor, and retinal pigment epithelial cells. The interphotoreceptor matrix is not a classic extracellular matrix, as it is more analogous to epithelial glycocalyces. Based on its strategic location, the interphotoreceptor matrix is generally considered to mediate biochemical and physical interactions between the neural retina and the retinal pigment epithelium. The two primary functions of the interphotoreceptor matrix are to promote retinal-retinal pigment epithelium adhesion, and maintain photoreceptor viability (1). Recent studies have provided compelling evidence that specific interphotoreceptor matrix glycoconjugates, most likely proteoglycans, participate in maintaining a normal retina-retinal pigment epithelium interface and are especially important in mediating

 1120-6721/001-03$01.50/0

retinal adhesion. Two of these proteoglycans, designated IPM150 and IPM200, have recently been cloned and sequenced. These two newly recognized components of the retina-retinal pigment epithelium interface belong to a novel family of proteoglycans and could also be present at the vitreo-retinal interface. If so, they may play an important role in vitreo-retinal adhesion, and the loss thereof during aging. Other observations, especially from studies of retinal development and degeneration, have suggested a role for the interphotoreceptor matrix in the maintenance of photoreceptor cell viability. Insoluble interphotoreceptor matrix has been identified in the vitreous of patients with rhegmatogenous retinal detachments and may be responsible for Shafer's sign, a clinical indication of retinal detachment. These same interphotoreceptor components exhibit distinct compositional changes that are correlated with macular drusen, the extracellular deposits in Bruch's membrane that are known to be a risk factor for the development of age-related macular degeneration in humans.

Another important extracellular matrix, located at the posterior aspect of the retina is Bruch's membrane. Although this structure is not technically part of the RPI, at least as defined above, it plays an important role in a major cause of blindness. Strategically situated between the retina and its major source of oxygen and nutrition, the choriocapillaris, this extracellular matrix is essential for normal retinal function. Indeed, a breakdown in presumed inherent anti-neovascular effects must play a role in early stages of choroidal neovascularization, as this extracellular matrix is the first barrier that falls when new vessels grow out of the choroid to invade the RPI in exudative age-related macular degeneration.

The retinal basal lamina lies adjacent to the corpus vitreus and is composed of type IV collagen closely associated with glycoproteins (2). At the pars plana, the basal lamina has a true lamina densa. Posterior to the ora serrata, the basal lamina of Mueller cells is actually the internal limiting lamina of the retina. Within the internal limiting lamina, the layer immediately adjacent to the Mueller cell is a lamina rara which is 0.03 - 0.06 um thick. At the rim of the optic disc the retinal internal limiting lamina ceases although the basal lamina continues as the "inner limiting membrane of Elschnig". This structure is 50 nm thick and is believed to be the basal lamina of the astroglia in the optic nerve head. At the central-most portion of the optic disc the membrane thins to 20 nm, follows the irregularities of the underlying cells of the optic nerve head and is composed only of glycosaminoglycans and no collagen. The peripheral 'shell' of the corpus vitreus courses posteriorly from the posterior border of the vitreous base and is known as the "posterior vitreous cortex". This structure is 100-110 um thick and consists of densely packed type II collagen fibrils and the highest concentrations of hyaluronan in the entire corpus vitreus. Although there are no direct connections between the posterior vitreous and the retina, the posterior vitreous cortex is quite adherent to the internal limiting lamina of the retina (3). The exact nature of the adhesion between the posterior vitreous cortex and the internal limiting lamina is not known, but most probably results from the properties of the various extracellular matrix molecules including laminin, fibronectin, and sulfated proteoglycans found at this interface. It is noteworthy that there are a number of important diseases that arise from vitreo-macular traction, perhaps because of unusual molecular morphology and pathophysiology at this interface (4).

Only a few studies have investigated whether there are similarities in how the extracellular matrix components at these two different sites change in aging and as a result of disease. The need to further our understanding of the normal structure and function of these interfaces and how they change in aging and disease is underscored by the following important consideration:

The most common cause of blindness in Americans aged 20-74 is diabetic retinopathy. In it's most severe form, this disease features the proliferation of abnormal blood vessels into the vitreo-retinal interface (2). The most common cause of blindness in older Americans and Western Europeans is age-related macular degeneration. The most severe form of this disease is characterized by the proliferation of abnormal blood vessels into the retina-retinal pigment epithelium Bruch's membrane interface. Although most experts might consider these two conditions as quite disparate, these two pathologies must share certain very similar biologic events. Both involve a breakdown in the normal mechanisms designed to inhibit neovascularization as well as powerful stimuli to promote angiogenesis. Hence, studies comparing the molecular composition and structural organization at these

interfaces will likely shed light on the former aspect, while comparisons of the inciting noxious stimuli in the two pathologies could provide insight into the latter aspect of this pathophysiology. Comparative studies such as these are likely to be rewarding and should be encouraged throughout the world.

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