Text S1

Biological Components and Processes in CNV

CNV involves the interaction of two fundamental structures, the retina with its supporting structures and the choriocapillaris. We briefly review the functional and structural properties of their components in the context of CNV.

Retina, RPE, Bruch's Membrane and CC

The retina consists of two concentric regions, the *inner retina* and the *outer retina* proper (Figure 1). Beneath the outer retina proper lies the retinal pigment epithelium (*RPE*), a monolayer of pigmented epithelial cells situated between the photoreceptors and the choroid. The RPE plays numerous roles in maintenance of the retina. Beneath the RPE, *Bruch's membrane* (*BrM*), a strong, multi-layered, 2-to-4-μm-thick porous membrane structurally stabilizes the RPE (Figure 1). The very dense choriocapillaris (or choroid) lies behind the outer retina, separated from it by BrM and the RPE.

The inner retina, adjacent to the vitreous humor, includes the inner retinal vasculature and layers of neural cells. The outer retina, adjacent to the RPE, includes the rod and cone photoreceptors. Each rod or cone cell has three regions along its axis in the direction perpendicular to the retinal layers: the *cell body*, the *photoreceptor outer segment* (*POS*), which contains the light-absorbing outer-segment disks, and the *photoreceptor inner segment* (*PIS*) (Figure 1). The ensemble of POSs forms a well-defined layer in the retinal plane. Similarly, the ensemble of photoreceptor cell bodies forms the outer nuclear layer (*ONL*) separated from the PIS layer (the ensemble of PISs) by a membrane called the *outer* (or *external*) *limiting membrane* (*OLM*). The OLM supports and orients the cells which cross it and impedes the extracellular diffusion of large molecules [1].

The properties of the retinal layers vary depending on the in-layer distance from the *fovea*. The outer retina is thinner in the *periphery* far from the fovea and thicker in the fovea, where the density of photoreceptors is higher and vision is most acute. CNV is most damaging when it occurs in the subfoveal area. In the central fovea, the inner retina is thinnest and lacks inner-retinal vasculature [2,3].

The thickness, porosity, elasticity and composition of BrM all change due to aging [4] (see [5], for a comprehensive review). Extracellular material (mostly waste byproducts from phagocytosis) accumulates between the RPE and BrM forming *basal deposits*. Basal deposits located between the RPE plasma membrane and its basement membrane (*RBaM*) are called *basal laminar deposits* (*BlamD*). Basal deposits external to the RBaM in the *inner collagenous layer* or *inner collagenous zone* are called *basal linear deposits* (*BlinD*). Deposits that appear clinically as yellowish-white spots in the retina are called *drusen*. *Hard drusen* are mechanically stiff nodular deposits with defined edges and do not strongly correlate with CNV [6]. *Soft drusen* are mechanically softer, have less defined sloping edges and correlate strongly with CNV.

CNV is usually limited to the sub-RPE space (*i.e.* between the RPE and BrM) and sub-retinal space (*i.e.* between the RPE and photoreceptors), though anastomosis of CNV capillaries with the inner-retinal vasculature occasionally occurs [7].

Oxygen Transport and Metabolism in the Retina

Two capillary beds supply oxygen and nutrients to most regions of the retina and remove waste products, the inner-retinal capillaries and the choriocapillaris (*CC*). The CC supplies more than 90 percent of the oxygen to the photoreceptors in dark-adapted conditions and almost 100 percent in light-adapted conditions [8]. The inner retinal capillaries supply oxygen to the inner layers of the retina, maintaining the oxygen partial pressure (PO_2) almost constant in both light and dark-adapted conditions [8,9]. The normal oxygen concentration at the OLM varies slightly, depending on the in-layer distance from the fovea.

The PIS is packed with mitochondria, so photoreceptors have the highest oxygen consumption rates of any cells in the human body. The metabolic activity and oxygen concentration of the photoreceptors depend on the intensity of light they receive. In dark-adapted conditions, photoreceptors consume oxygen at about twice their light-adapted rates.

Adhesion Properties of the RPE, POS and PIS

The lipid bilayer forming the cell membrane is flimsy and cannot, by itself, transmit large forces from cell to cell or from cell to *extracellular matrix* (*ECM*). *Anchoring junctions* solve this problem by forming strong membrane-spanning structures that tether inside the cell to the tension-bearing filaments of the cytoskeleton.

RPE cells are apicobasally polarized. On the lateral surfaces of RPE cells, two *bands of epithelial adhesion junctions* connect to neighboring RPE cells (Figure 2). On the apical- most lateral surfaces of RPE cells, a band of *tight junctions* (*TJ*s) (z*onula occludens, ZO, Mesh*) seal adjacent RPE cells together, forming the outer blood-retina (*oBRB*) barrier and restricting transport of material (*e.g.* albumin) into and out of the retina [10-12]. On the lateral surfaces of RPE cells, basal to the TJs, *adherens junctions* (*AJ*s) form another junctional band that goes all the way around each cell and mechanically connects the cytoskeleton of each RPE cell to the neighboring RPE cells, giving structural integrity to the RPE. RPE cells form AJs predominantly via N-cadherins [13,14] (RPE cells also produce a small amount of E-cadherin, the most common adhesion molecule in the AJs of most other epithelial tissues). In addition to these junctional bands, *desmosome plaques* (*DP*s) and *gap junctions* distributed on the lateral surfaces of the RPE cells connect neighboring RPE cells. Desmosomes are crucial for tissue integrity, resist calcium-depletion in developed tissue and help to resist shearing forces. When we refer to e*pithelial junctions* without further qualification, we refer to the ensemble of junctional structures that participate in RPE-RPE adhesion, including TJs, AJs and DPs. The basal surfaces of RPE cells adhere to the very thin *basal laminae* of the RBaMs so strongly that the basal laminae behave like extensions of the cells' plasma membranes [15]. *Intergrins* mediate RPE-basal lamina adhesion. The RBaMs attach to the inner collagenous layer of BrM via microfibrils passing through both the elastic layer of BrM and the RBaMs [15,16]. When we refer to the *RPE-BrM complex*, we refer to the RPE-RBaM-BrM ensemble. Soft drusen reduce the adhesion

between the RBaMs and the inner collagenous zone (Figure 1) of BrM and correlate with localized detachment of the RPE from BrM [6,17-19]. Age-related modifications of BrM, especially soft drusen, also inhibit reattachment of transplanted RPE cells to BrM [20,21].

Photoreceptors pass spent photo-sensitive disks to the apical processes of RPE cells. This apical contact attaches photoreceptors to the RPE [22-24] more weakly than would RPE-RPE epithelial adhesion or attachment of RBaMs to BrM, so detachment of photoreceptors from the RPE (*retinal detachment*) due to impact is more likely than *RPE tears* (which break RPE-RPE epithelial junctions) or *RPE detachment* (which breaks RBaM-BrM attachment). Disruptions of RPE-POS contact affect not only the integrity of the oBRB, they also induce pathological cell growth and division in the RPE [25-27], disrupting the RPE epithelial structure and preventing successful therapeutic retinal reattachment (see Table 1).

Photoreceptors have limited or no motility and are held together in constant positions by multiple ECM components in the outer retina and OLM, ensuring consistant positional mapping of the visual field to the photoreceptors and the corresponding neurons in the visual cortex (*somatotopic mapping*). This somatotopic consistency is crucial to the development and maintenance of high-resolution visual perception.

Angiogenic and Antiangiogenic factors

Since laterally adjacent RPE cells form tight junctions, factors secreted by the photoreceptors on the apical side of the RPE do not pass through an intact RPE epithelial sheet to affect the choriocapillaris or CNV capillaries. The RPE secretes two VEGF-A isoforms from its basolateral surfaces to maintain the CC. VEGF-A_{120} diffuses freely and does not bind to heparin-sulfate. More than 75% of RPE-derived VEGF is the VEGF-A_{165} isoform [28] which has a weak affinity for heparin-sulfate, allowing it to diffuse across BrM while remaining resident long enough to bind to the VEGF receptors of the CC (otherwise the constant fluid flow from the vitreous humor to the CC and the high rate of CC blood flow would elute the VEGF before it bound to the EC's VEGF receptors). Mutant mice producing only VEGF-A_{188}, which binds strongly to extracellular matrix and therefore has a short diffusion length, develop a normal CC but suffer CC atrophy and RPE and BrM abnormalities, leading to RPE loss and dramatic choroidal remodeling beginning at 7 months [29], suggesting that RPE-derived free-diffusing VEGF-A isoforms are necessary to maintain the choriocapillaris. These VEGF isoforms may also help support other retinal cell types. When we refer to VEGF-A without qualifications, we mean VEGF-A_{165}, which appears to play the dominant role in CNV. In addition to RPE-derived VEGF-A, ECs, in general, produce multiple isoforms of VEGF-A, among which short-diffusing isoforms can serve as autocrine chemoattractants, playing a key role in capillary patterning (for a detailed discussion of capillary patterning mechanisms, see [30,31]). In many cases, ECs can only sense ECM-bound isoforms of VEGF-A when they are released from the ECM by matrix-degrading enzymes.

Since the retina is the most metabolically active tissue in the body, the density of capillaries in the CC is unusually high. The CC has small inter-capillary distances (~ 20 μm) [32,33] compare to typical inter-capillary distances (~ 100 μm to 200 μm). Since RPE-derived VEGF is essential for to maintain this dense population of ECs in the CC, we hypothesize that RPE-derived VEGF secretion must be substantial. The denser population of ECs consuming RPE-derived VEGF

globally balances the higher secretion rate of RPE-derived VEGF. However, because of inhomogeneities in the CC-BrM-RPE complex [16], we hypothesize that RPE-derived VEGF does not diffuse uniformly, producing relatively high local concentrations of RPE-derived VEGF, sufficient to maintain a substantial population of activated ECs in the CC even in the healthy retina.

RPE cells also produce the antiangiogenic *pigment-epithelium-derived factor* (*PEDF*). At homeostasis, proangiogenic and antiangiogenic factors balance. In the aged human retina, PEDF has a spatial distribution similar to that of VEGF-A [34].

Numerous other diffusible pro and antiangiogenic factors [35,36] may help modulate capillary behavior, but we do not consider them in this paper (see also the *Inflammation* subsection below). While angiogenesis requires proangiogenic factors to dominate antiangiogenic factors, normal angiogenesis requires the factors to remain in rough balance. In pathological situations, when the levels of proangiogenic factors are too large relative to antiangiogenic factors, the resulting vessels do not mature and remain leaky and insufficient at oxygen and nutrient transport.

Angiogenesis and BrM Degradation

High levels of VEGF-A activate normally quiescent endothelial cells in blood vessels. Via a Delta/Notch contact-inhibition selection mechanism, small populations of these activated ECs become *tip cells* which lead angiogenic *sprouts* up gradients of VEGF-A [37,38]. A morphologically distinct population of activated ECs called *stalk* cells form the body of these angiogenic sprouts. While tip and stalk cells are distinct at any instant, they can dynamically exchange identities [39]. Macrophages and other immune cells can substitute for tip cells in their pathfinding role. Tip cells have very low rates of proliferation, while stalk cells proliferate at moderate rates.

Excess proteolytic activity of macrophages and activated endothelial cells can cause focal thinning of BrM [40-44]. Tip cells and immune cells express a number of matrix degrading enzymes which locally break down ECM and BrM, while BrM is continuously reformed by poorly understood means. RPE cells also secrete numerous inactive MMPs and tissue inhibitor of mellapoteinases (*TIMP*s) that inhibit activated MMPs [45-49]; *E.g.*, tip cells and macrophages express transmembrane type-1 MMP (*MT1-MMP*) which activates MMP-2, which plays a key role in tip-cell and macrophage migration and breakdown of basement membrane in tumor invasion [50-54]. A similar mechanism is plausible for tip-cell and immune-cell breakdown of BrM.

Inflammation

Inflammation and immune cells play major roles in CNV. Macrophages in normal retina remove debris accumulated in BrM [55], helping to maintain normal retinal structure and function. However, chronic or excessive acute inflammation can promote CNV initiation and impair the integrity of the RPE, promoting CNV progression. Irregularities in regulation of the complement cascade and overactivity of immune cells may perturb RPE cells, causing them to form more

basal deposits (both soft and hard drusen), which in turn induce a stronger immune response which can initiate angiogenesis [56,57]. *Angiopoietin-2*, a key proangiogenic inflammatory factor, activates quiescent ECs with a response modulated by local VEGF concentrations and increases ECs' directional motility. *Angiopoietin-1*, on the other hand, inhibits activation of ECs and helps newly-formed vessels mature [58]. Pro-inflammatory cytokines, *e.g.*, tumor necrosis factor alpha (*TNF-α*) and *interleukin-1β* and *-8*, result in extensive breakdown of both the oBRB and inner blood-retinal barrier (*iBRB*) which separates inner-retinal capillaries from the outer retina [12,59-62].

Inflammation may affect early and late-stage CNV by weakening RPE-RPE and RPE-POS adhesion. Inflammation also impairs the juxtacrine Delta/Notch inhibitory signaling which couples adjacent ECs and normally promotes ECs quiescence and inhibits tip-cell selection, increasing EC activation [63].

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