Chapter 8
Extracellular Matrix Alterations and Deposit Formation in AMD

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Abstract Age related macular degeneration (AMD) is the primary cause of vision loss in the western world (Friedman et al., Arch Ophthalmol 122:564–572, 2004). The first clinical indication of AMD is the presence of drusen. However, with age and prior to the formation of drusen, extracellular basal deposits accumulate between the retinal pigment epithelium (RPE) and Bruch's membrane (BrM). Many studies on the molecular composition of the basal deposits and drusen have demonstrated the presence of extracellular matrix (ECM) proteins, complement components and cellular debris. The evidence reviewed here suggests that alteration in RPE cell function might be the primary cause for the accumulation of ECM and cellular debri found in basal deposits. Further studies are obviously needed in order to unravel the specific pathways that lead to abnormal formation of ECM and complement activation.

Keywords AMD · Extracellular matrix · basal deposits · RPE · Drusen · Complement system · Inflammation · MMP

8.1 Introduction

Macular degenerations (MDs) are disorders that include both inherited forms and the more prevalent age-related forms. AMD is the most common form of MD and is the primary cause of vision loss in the western world (Friedman et al. 2004). Although it is a prevalent disease, the initiation and pathogenesis are not well understood. The success of the treatments for AMD is limited (Lotery and Trump 2007; Miller 2013).

MDs are considered disorders of the RPE/BrM/choroid complex (Hageman and Mullins 1999). BrM is a specialized ECM located between the RPE and choroid. RPE cells secrete the proteins of BrM and have a role in the regulation of their

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turnover (Campochiaro et al. 1986; Chen et al. 2003; Aisenbrey et al. 2006). Structure and functions of BrM have recently been reviewed (Curcio and Johnson 2013). Briefly, BrM consists of five layers: RPE basal lamina/inner collagenous layer/elastin layer/outer collagenous layer/basal lamina of choriocapillaris. The major matrix structural proteins of BrM include collagens I-VI, elastin, perlecan (heparin sulfate proteoglycan), laminin and nidogen. Also present in BrM are matricellular proteins and associated proteins. Matricellular proteins contribute to cell-matrix interactions and RPE cell responses and include thrombospondin 1, fibulins, TGF-beta (Bornstein and Sage 2002). Growth factors comprise one class of associated proteins. In addition to the structural role of BrM, it has a critical role in signaling and provides barrier and filtering functions.

8.2 Extracellular Matrix, More than a Mere Structural Scaffold

ECMs are highly organized structures of proteins that cells secrete in order to create and maintain proper tissue architecture. The ECM structures are determined largely by composition, hence any alteration in composition will likely affect function (Davis et al. 2000; Paszek and Weaver 2004; Hynes 2009). ECMs are not static structures; studies in cancer, fibrosis and myocardial diseases demonstrated that ECM undergoes continuous dynamic remodeling (Cox and Erler 2011; Iijima et al. 2011; Rienks et al. 2014). Remodeling is regulated by a group of zinc-dependent endopeptidases called matrix metalloproteinases (MMPs) and their inhibitors, tissue-inhibitor of metalloproteinases (TIMPs) (Matrisian 1992). MMPs are capable of degrading all of the structural elements of the ECM, but also can process cytokines, growth factors, chemokines, and receptors on the cell membranes (Chang and Werb 2001; Van Lint and Libert 2007). MMPs have been shown to regulate not only the ECM turnover but signaling pathways as well (Hu and Ivashkiv 2006; Dufour et al. 2008; Glasheen et al. 2009). In BrM, signalling to the RPE cells occurs through interactions of integrins with laminin in BrM (Campochiaro et al. 1986; Chen et al. 2003; Aisenbrey et al. 2006).

MMP activity is tightly regulated by specific inhibitors, TIMPs (Nagase and Woessner 1999; Bergers and Coussens 2000). Impairment of the endogenous activity of the MMP/TIMP complexes causes pathologies such as tumor progression, rheumatoid arthritis, heart diseases, blood vessel diseases and atherosclerosis (Liotta et al. 1991; Gomis-Ruth et al. 1997; Chang and Werb 2001). Ocular diseases to which impaired MMP/TIMP balance contributes include retinal dystrophy, retinitis pigmentosa, AMD, inherited MD and diabetic retinopathy (Jones et al. 1994; Fariss et al. 1998; Nita et al. 2014). In AMD, TIMP3 accumulates in BrM (Kamei and Hollyfield 1999).

8.3 Macular Degenerations: Alterations in Bruch's Membrane and Deposit Formation

With age and before the presence of clinical evidence of macular disease, histopathological studies show BrM becomes thickened and extracellular basal deposits develop between the RPE and BrM (Kliffen et al. 1995; Kliffen et al. 1997; Reale et al. 2009). Basal deposits, accumulations of extracellular material in BrM and between BrM and the RPE are called basal linear (BLinD) or basal laminar deposits (BLamD), respectively (Sarks 2007; Curcio and Millican 1999; Sarks et al. 1976). BLamD, composed of granular material with wide-spaced collagen are located between the plasma membrane and the basal lamina of the RPE (Green and Enger 1993). BLamD are also a common feature in mouse models used to study AMD (Malek et al. 2003; Espinosa-Heidmann et al. 2006; Fu et al. 2007; Fujihara et al. 2009). BLinD, characterized by coated and non-coated vesicles composed of membranous material are located in the inner collagenous layer of BrM (Loeffler and Lee 1998; Curcio and Millican 1999). BLamD and BLinD as well as drusen all contain varying amounts of ECM proteins, complement components or complement regulators and inflammatory proteins (Hageman and Mullins 1999; Crabb et al. 2002; Chong et al. 2005; Sivaprasad et al. 2005; Lommatzsch et al. 2008; Wang et al. 2010). Proteomic analysis of BLamD in a mouse model of an inherited MD confirmed the presence of ECM/BrM components (Garland et al. 2014). The mechanisms of how any of these deposits form are essentially unknown. The presence of ECM proteins in all types of sub-RPE basal deposits provides strong evidence for a role of dysregulation of ECM in MD. The presence of complement and inflammatory proteins in drusen led to the conclusion that the complement system plays a direct role in drusen biogenesis (Mullins et al. 2000; Hageman et al. 2001; Anderson et al. 2002). In fact, in a mouse model the formation of BLamD was inhibited in the absence of an active complement system (Garland et al. 2014).

8.4 RPE Dysfunction and Aberrant ECM

What needs to be revealed is whether RPE dysfunction leads to ECM alterations and basal deposit formation or whether changes in ECM/BrM lead to RPE dysfunction and formation of aberrant ECM, and how inflammation and complement become involved.

Any process that disrupts signaling pathways between BrM and RPE could induce altered RPE function, including expression and secretion of ECM, and altered expression and secretion of MMPs and TIMPs (Leu et al. 2002; Kortvely et al. 2010; Hussain et al. 2011). Altered secretion of MMPs and TIMPs would likely lead to altered ECM turnover and ultimately to altered ECM composition. While the presence of basal deposits will almost certainly disrupt signaling pathways between BrM and RPE they could also be the consequence of disrupted signaling (Leu et al. 2002; Kortvely et al. 2010; Hussain et al. 2011).

The process of degradation of the ECM by MMPs generates matrikines, some of which can provoke an inflammatory response (Davis et al. 2000; Egeblad and Werb 2002; Sorokin 2010; Iijima et al. 2011). This is supported by the observation that matrikines derived from collagen I, collagen IV, fibronectin, laminins, elastin, nidogen, and thrombospondin-1 and −2 that exhibit chemotactic activity for inflammatory cells have been found in the sub-RPE deposits (Adair-Kirk and Senior 2008). There is evidence that MMPs can degrade these proteins and may be involved in generating the matrikines (Guo et al. 1999; Zhuge and Xu 2001; Marin-Castano 2005). However, evidence has been presented for increased and decreased MMP activity (Guo et al. 1999; Hussain et al. 2011). Alternatively, an altered composition of the ECM could alter its structure exposing neo-epitopes that could engage the complement system or the accumulation of ECM proteolytic fragments and other debris along the interface of the RPE and BrM might lead to complement activation.

While changes in BrM are the earliest age-related changes observed, the role of the RPE in expression and secretion of the ECM components of BrM and in the regulation of its turnover suggest that altered RPE cell function might be the primary cause for the accumulation of ECM and cellular debri found in basal deposits. The altered RPE cell function could be caused by any of the proposed processes such as oxidative stress or mutations that are thought to lead to macular degeneration (Marin-Castano 2005).

Further studies are needed in order to unravel the specific pathways that lead to abnormal formation of ECM and complement activation and the formation of drusen. Understanding these mechanisms should be extremely helpful in identifying targets for new AMD therapies.

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