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Review

Therapeutic Role of Extracellular Matrix (ECM):Understanding Lens Development and Pathological Perspective

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ABSTRACT

Human diseases caused by mutations in extracellular matrix genes are often associated with an increased risk of cataract and lens capsular rupture. However, the underlying mechanisms of cataract pathogenesis in these conditions are still unknown. This review provides a brief overview of the function and structure of the extracellular matrix and reviews the progress that has been made in understanding the involvement of extracellular matrix in lens development and pathology.

Keywords: Lens development, ECM, Lens capsular rupture, pathology

The lens constitute an important model for investigating and understanding molecular and cellular mechanisms that underlie inductive interactions during development. These mechanisms have been shown to be relevant for understanding pathogenesis of cataract. Much progress has been made in elucidating many of the growth factor signalling pathways and transcription factors involved in these processes. However, the interactions between lens cells and their unique extracellular matrix (ECM), the lens capsule, have been poorly studied.

The cataract can be a multifactorial disease and is often associated with systemic or genetic disorders, such as diabetes and Lowe syndrome (1–3). Notably, human diseases caused by mutations in extracellular matrix (ECM) 4 genes are also often associated with an increased risk of cataract. Stickler and Marshall Syndromes are two disorders caused by mutations in the COL2A1 gene that are associated with the early onset of distinctive cataracts (4, 5). Alport syndrome, caused by mutations in either the COL4A3, COL4A4, or COL4A5 genes, is also associated with lens capsule abnormalities and cataract formation (6–8). Humans

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carrying mutations in the COL4A1 locus often exhibit lens abnormalities and cataracts along with porencephaly and sporadic intracerebral hemorrhage (9–13). To date, approximately 13 independent mutations in the mouse Col4a1 locus and three independent mutations in mouse Col4a2 locus have been found to cause vascular cataract and lens abnormalities in mice (14–16). However, the underlying mechanisms of cataract pathogenesis resulting from these collagen mutations are still unknown.

This review provides a brief overview of the function and structure of the extracellular matrix and reviews the progress that has been made in understanding the involvement of extracellular matrix in lens development and pathology. It is hoped that this review will stimulate further research into these important subject – ECM- and help focus efforts on the many unanswered questions about its role in lens biology and pathology.

Lens Structure:

Structurally the lens consists of capsule, epithelium and fiber cells (Fig. 1). The lens epithelial cells (LEC) migrate and terminally differentiate into fibers by losing their nucleus. This terminally differentiated lens fiber cells are forced toward the core of the lens. The embryonic fiber that developed and accumulated in the center of the lens in the early embryonic stage is termed as embryonic nucleus, whereas the other two layers formed after the embryonic nucleus are known as juvenile and adult nucleus. The outermost part of the lens fibers are termed as cortex and seen as a series of concentric layers (17). The whole cortex and epithelium are lodged in the capsule, which is cellular in nature but allows transfer of ions and nutrients across. As no cells are shed, the lens demonstrates cells at varying states of senescence and is remarkable for its ability to preserve its specialized function of transparency throughout the life span. The opaque tissue in any part of the clear lens containing transparent crystalline protein in the human eye is identified as cataract. Generally cataract is considered as a multifactorial old age, disease; however, it may be present in neonates or may develop at any time in the life span of an individual. Based on the position of the opacity various forms of cataracts have been identified, nevertheless progressive development of opacity covers whole lens and thus results in blindness. Therefore, the study of the lens and cataract also help us to understand the ageing process.

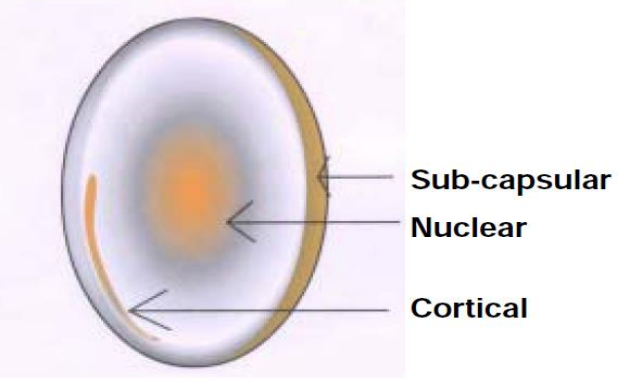

Fig. 1: Schematic drawing of the lens. The lens gradually becomes aged, denatured and opaque without any pathogenic or local causes usually it occurs on both the eyes but onset time may differ. Clinically nuclear sub capsular (SC) is common, however may be cortical and posterior sub-capsular takes part in fully developing SC.

Lens Development and Growth:

Initiation of lens formation during embryogenesis is the result of a series of inductive interactions (18, 19) Ocular morphogenesis commences when bilateral imaginations of the embryonic forebrain, the optic vesicles come into contact with the overlying head ectoderm. In this region of intimate contact, the ectoderm thickens to form the lens placode and the neuroepithelium forms the retinal disc. Coordinated invagination of these structures, forms the lens pit and optic cup, respectively. The optic cup differentiates into neural retina, ciliary body, and iris, whereas the lens pit separates from

overlying ectoderm to form the lens vesicle. Posterior vesicle cells, responding to signals from the optic cup, elongate and differentiate as primary fiber cells, whereas the anterior vesicle cells remain as a cuboidal epithelial monolayer (18–20). Thus, the mature lens is composed of two cell types (epithelial and fiber), enclosed by a basement membrane, the lens capsule. Continued growth of the lens occurs through epithelial cell proliferation, migration, and differentiation into fiber cells. In the postnatal lens most of the anterior epithelial monolayer is quiescent, with proliferation being largely restricted to a region just anterior to the lens equator, called the germinative zone. Progeny of these divisions either contribute to the epithelium or move posteriorly across the lens equator, into the transitional zone where they undergo fiber differentiation, which is characterized

By extensive elongation and structural specializations, as well as the accumulation of fiber specific proteins such as β- and γ-crystallins. As terminal differentiation proceeds, fibers lose their organelles and nuclei, via either apoptotic (apoptosis) or autophagic mechanisms (21–24).These processes of proliferation, migration and differentiation continue throughout the life of the lens, with cells being continually added to the fiber mass and, under normal circumstances, no cells are lost from the lens (19,20).

There is considerable evidence that lens growth and cell behaviour are regulated by growth factors resident in the two major ocular media (aqueous and vitreous humors) and derived from various ocular tissues, particularly the retina, ciliary body, iris, and the lens itself (21, 24). The presentation of growth factors to the two lens compartments (epithelial and fiber) has been shown to be of critical importance in maintaining lens polarity and growth patterns. In particular, members of the FGF family are present in an antero-posterior gradient in the eye, which regulates patterns of epithelial cell proliferation, migration and differentiation. Both the MAPK and PI3K signalling pathways have been implicated as downstream mediators of FGF-induced proliferation and differentiation (24, 25). While FGFs are the only known family of growth factors that can induce the change of epithelial to fiber cell phenotype, members of the TGFβ and Wnt growth factor families are also involved in various stages of lens development, and mitogens such as IGF, EGF, and PDGF induce proliferation of the epithelial cells (24, 25).Moreover, several growth factors (e.g. IGF, Wnt) can act synergistically with FGF to regulate differentiation and crystalline synthesis (26, 27). TGFβ family has dichotomous effects on the lens: BMP and TGF receptor signalling has been implicated in terminal stages of fiber differentiation (28), but all three mammalian isoforms of TGFβ (TGFβ1, β2, and β3) can induce lens epithelial cells (LEC) to undergo an epithelial mesenchymal transition (EMT) that is characteristic of changes in human anterior sub-capsular cataract (ASC) and also posterior capsule opacification (PCO), which occurs following cataract surgery (29).

Cell–ECM Interactions in the Lens:

Both epithelial and fiber cells are intimately associated with a thick basement membrane, which encapsulates the lens and separate cells from the ocular media. Thus, signalling molecules from the ocular media must traverse the lens capsule matrix before stimulating receptors on the cell surface. As the lens differentiates, there are concomitant changes in the capsule matrix, suggesting that it plays dynamic roles in lens development. Similarly, in ASC, there are significant alterations in the lens capsule matrix that accompany aberrant cell behaviour, indicating an involvement of cell–ECM interactions in lens pathology.

Collagen: Initiation of lens formation during embryogenesis is the result of a series of inductive interactions (18, 19). Ocular morphogenesis commences when bilateral imaginations of the embryonic forebrain, the optic vesicles come into contact with the overlying head ectoderm. In this region of intimate contact, the ectoderm thickens to

form the lens placode and the neuroepithelium forms the retinal disc. Coordinated invagination of these structures, forms the lens pit and optic cup, respectively. The optic cup differentiates into neural retina, ciliary body, and iris, whereas the lens pit separates from overlying ectoderm to form the lens vesicle. Posterior vesicle cells, responding to signals from the optic cup, elongate and differentiate as primary fiber cells, whereas the anterior vesicle cells remain as a cuboidal epithelial monolayer (18-20). Thus, the mature lens is composed of two cell types (epithelial and fiber), enclosed by a basement membrane, the lens capsule. Continued growth of the lens occurs through epithelial cell proliferation, migration, and differentiation into fiber cells. In the postnatal lens most of the anterior epithelial monolayer is quiescent, with proliferation being largely restricted to a region just anterior to the lens equator, called the germinative zone. Progeny of these divisions either contribute to the epithelium or move posteriorly across the lens equator, into the transitional zone where they undergo fiber differentiation, which is characterized by extensive elongation and structural specializations, as well as the accumulation of fiber specific proteins such as β- and γ-crystallins. As terminal differentiation proceeds, fibers lose their organelles and nuclei, via either apoptotic or autophagic mechanisms (21-23). These processes of proliferation, migration and differentiation continue throughout the life of the lens, with cells being continually added to the fiber mass and, under normal circumstances, no cells are lost from the lens (19, 20).

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Laminin, Fibronectin and Yimentin: Laminins are heterotrimeric proteins, comprised of α, β and γ chains and recent experiments with isoform-specific antibodies demonstrated the presence of α1 chain in adult murine lens (30), and α1, α5, β1, and β2 chains in fetal human lenses (31). While mice that are deficient in any of the α1, β1, or γ1 chains are embryonic lethal at implantation or gastrulation (32), recent morpholino knockdown experiments in zebrafish show that α1 laminin is essential for lens differentiation. The lens vesicle forms, but subsequent development is arrested and cells degenerate rapidly (33). Lens phenotypes have also been observed in zebrafish with insertional mutations of the β1 and γ1 laminin genes (34). Mutations in the human β2 chain of laminin have been found to cause Pierson syndrome, a congenital nephrotic syndrome with ocular abnormalities including posterior lenticonus (35, 36).

Fibronectin is detected at early stages of rat lens morphogenesis and there is indirect evidence for a functional role from studies in which RGD (arginine-glycine-aspartate) peptides, injected into the optic lobes during early chick lens development, caused failure of optic cup and lens invagination (37). During rat lens differentiation there is a decrease in fibronectin reactivity in the capsule from E16 and absence by E19 (41). This developmental loss of reactivity correlates with a loss in capacity of epithelial cells to migrate on fibronectin in vitro (41). More recent studies indicate that fibronectin is also present in the postnatal mouse lens capsule ((38, 39), Wederell, unpublished observations). However, its localization in the exterior layer of the anterior capsule that faces the aqueous humor (38) suggests that it may not affect or be derived from lens cells. The fibronectin-null mouse is embryonic-lethal soon after gastrulation (40), so the role of fibronectin in the lens is not known.

Vimentin is a major component of lenticular cytoskeletal intermediate filament protein and is also an essential pre requisite for the establishment of filament network in lens fiber cells. The over expression of vimentin in the lenses of transgenic mice interferes with normal differentiation of lens fibers which results in the impairment of cell denucleation and elongation process that leads to cataractogenesis. Normally in the mature lens fiber cells, vimentin are not expressed. Thus the over expression of vimentin may lead to the formation of SC.

Entactin/nidogen and Tenascin: Entactin/nidogen comprises three globular domains and a rod-like domain with EGF repeats. It binds laminin, collagen IV and HSPG and is thought to function in stabilizing the supra molecular structure of basement membranes (43-45) There are two forms (entactin-1 and entactin-2), but only entactin-1 is expressed in lens (46), particularly at the vesicle stage (47). Mice with a null mutation of entactin-1 have abnormal thinning and discontinuities of basement membranes in various tissues. In the lens, the posterior capsule is invaded by fiber cell processes and fiber suture formation is disrupted, but lenses remain clear (46). Tenascin, has been identified in the developing chick lens (42, 48),but is reported to not be normally expressed in mammalian lens, except in ASC (49-51).

Sulfated Proteoglycans: Heparan sulphate proteoglycans (HSPG) are components of the basement membrane that bind other ECM molecules, such as collagen and fibronectin, and function in the presence of growth factors to lens cells. Four species of HSPG are present in the rat lens capsule and all bind FGF1 and FGF2 with similar affinity. Although there is no difference in the distribution of different HSPGs between the anterior and posterior regions of the lens capsule (63), only the posterior capsule has detectable biological FGF activity (52). This differential sequestration and presentation of FGF activity within the lens capsule may be due to the different arrangement of HSPG laminae within these two regions of the capsule (53).

Chondroitin sulphate proteoglycan has also been detected and shown to play a role during invagination of the lens primordium. Treatment of early chick embryos with β-D-xyloside, so as to inhibit glycosaminoglycan synthesis, or with chondroitinase AC inhibited lens placode invagination (54).

Secreted Protein Acidic and Rich in Cysteine (SPARC): A more recently identified player in the regulation of the lens capsule is Secreted Protein Acidic and Rich in Cysteine (SPARC). This matricellular protein is thought to play a role in wound healing, tumour progression and cell proliferation by influencing cell adhesion, cytoskeletal organization and expression of ECM proteins (55, 56). SPARC has been localized to lens capsule, epithelial cells and early elongating fiber cells (55, 57, 58). SPARC-null mice develop cataracts by 3–4 months of age due to disruption of lens cell growth (55), particularly at the equator (59). During postnatal growth in these mutants there are altered cell–ECM interactions, characterized by

protrusion of cell processes into the lens capsule (55, 60). Similar to those seen in entactin-null mice. Recent studies indicate abnormal expression of laminin (61) and collagen IV (62) in SPARC null lenses, and the colocalization of laminin and SPARC in the endoplasmic reticulum of wild-type LEC suggests that SPARC may play a role in ECM secretion (61) by influencing cell adhesion, cytoskeletal organization and expression of ECM proteins (55,56). SPARC has been localized to lens capsule, epithelial cells and early elongating fiber cells (55, 57, 58). SPARC-null mice develop cataracts by 3–4 months of age due to disruption of lens cell growth (55), particularly at the equator (59). During postnatal growth in these mutants there are altered cell–ECM interactions, characterized by protrusion of cell processes into the lens capsule (55, 60), similar to those seen in entactin-null mice. Recent studies indicate abnormal expression of laminin (61) and collagen IV (62) in SPARC null lenses, and the colocalization of laminin and SPARC in the endoplasmic reticulum of wild-type LEC suggests that SPARC may play a role in ECM secretion (61).

Thrombospondin-1: Thrombospondin-1 (TSP-1) is a glycoprotein involved in activation of latent transforming growth factor beta (TGFβ) expression. There is TSP-1 expression in uninjured human and mouse lens epithelial cells and their fibrous tissue. In contrast, into post-operative lens cells differentiating to fiber cells, its expression levels decline.

Integrin: Integrins are a large family of glycosylated, heterodimeric, transmembrane, cell adhesion molecules that mediate principally cell–ECM interactions, but are also implicated in cell–cell interactions. Each heterodimer consists of one α and one β subunit that associate non-covalently through their extracellular domains to produce a functional receptor. To date, 18 α and 8 β mammalian subunits have been described and are known to form 24 distinct receptors (Table 1) that each bind to a specific ligand or set of ligands (64-66). Most integrin subunits have a large extracellular domain, a transmembrane segment and a short cytoplasmic domain that interacts with an actin-based cytoskeleton. Integrins are capable of both ‘inside-out’ (responding to signals from within the cell, which regulate integrin activity on the surface) and ‘outside-in’ (transmission of extracellular signals) signalling. Upon integrin activation and engagement of the ligand-binding domain, integrins cluster on the cell surface forming a focal adhesion or focal contact, which is essential for subsequent initiation of ‘outside-in’ signalling. The binding of ligands to integrins is via specific recognition sequences on the ligand, of which the RGD sequence is the prototypicexample. Integrins can bind a large number of ligands, including extracellular matrix molecules and other cell adhesion molecules (Table 1). The factors that determine ligand binding are many and complex. A major contributor to ligand specificity is the different combinations of α and β subunits. Another factor that affects ligand binding is the presence of divalent cations, in particular calcium, magnesium and manganese (Mg^{2+} and Mn^{2+} generally increase, whereas Ca^{2+} decreases affinity), which bind to motifs in the extracellular domain of α subunits. This region consists of seven repeat domains, arranged in propeller-like structures, which together with a similar conserved domain in the β subunit is involved in ligand binding (64, 66–68).

The lens has been shown to express several integrin subunits at various stages of development. Expression surveys noted expression of α2 [81] and α6A (69) subunits in embryonic mouse lens, as well as many other tissues. Studies of embryonic chick lens showed the presence of α3 and α6 but not α1, α5 or αv subunits (70).

Low levels of α1 subunit have been detected in the equatorial region of embryonic chick lens (71) and in a recent preliminary report (72) it has been detected in developing mouse lens. Variable expression of α2 subunit was detected in cell lines derived from human and rabbit LEC (73) and mRNA expression has been detected in postnatal mouse lens epithelium. A recent study (74) indicates that α2 is weakly localized in developing fibers from

E12.5 to E18.5 and in epithelial cells at E 18.5. However, no pathogenesis of cataract. The present study reviewed that the ECM influenced the proliferation and development of lens. Further studies need to identify the importance of ECM in the development and proliferation of the lens.

Conclusions:

The lens constitutes an important model for investigating and understanding molecular and cellular mechanisms that underlie inductive interactions during development. These mechanisms have been shown to be relevant for understanding reactivity was detected in adult lens. A lens phenotype has not been noted in α2 null mice (75), but this has not been investigated in detail.

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Conflict of Interest:

Authors declared no any conflict of interest.

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