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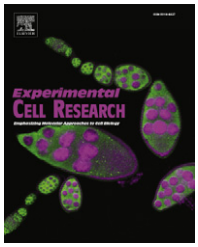

Review Article

The role of cell–extracellular matrix interactions in glomerular injury

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ABSTRACT

Glomerulosclerosis is characterized by excessive deposition of extracellular matrix within the glomeruli of the kidney, glomerular cell death, and subsequent loss of functional glomeruli. While in physiological situations the levels of extracellular matrix components are kept constant by a tight balance between formation and degradation, in the case of injury that results in fibrosis there is increased matrix deposition relative to its breakdown. Multiple factors control matrix synthesis and degradation, thus contributing to the development of glomerulosclerosis. This review focuses primarily on the role of cell–matrix interactions, which play a critical role in governing glomerular cell cues in both healthy and diseased kidneys. Cell–extracellular matrix interactions are made possible by various cellular receptors including integrins, discoidin domain receptors, and dystroglycan. Upon binding to a selective extracellular matrix protein, these receptors activate intracellular signaling pathways that can either downregulate or upregulate matrix synthesis and deposition. This, together with the observation that changes in the expression levels of matrix receptors have been documented in glomerular disease, clearly emphasizes the contribution of cell–matrix interactions in glomerular injury. Understanding the molecular mechanisms whereby extracellular matrix receptors regulate matrix homeostasis in the course of glomerular injury is therefore critical for devising more effective therapies to treat and ideally prevent glomerulosclerosis.

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Introduction

Glomerulosclerosis, the process by which glomerular tissue is replaced by extracellular matrix (ECM), is the final common pathway for loss of functioning glomeruli. Glomerulosclerosis occurs when the normal response to renal injury, characterized by the synthesis, degradation, and remodeling of ECM components, is dysregulated such that matrix deposition prevails on its breakdown.

The glomerulus, the filtering unit of the kidney, has a complex structure which includes: 1) a capillary bed composed of specialized fenestrated endothelial cells; 2) mesangial cells, the principal mesenchymal cell type, which maintain the three-dimensional structure of the capillary bed; 3) terminally differentiated visceral epithelial cells called podocytes; and 4) the glomerular basement membrane (GBM) that separates the podocytes from the endothelial cells (Fig. 1). The endothelial cells, GBM, and podocytes form the glomerular filtration barrier. Dysfunction of any of the four major components of the glomerulus due to genetic disorders, immune complex mediated injury, hemodynamic injury, or direct cytotoxic injury to specific glomerular cell components can result in glomerulosclerosis. Thus, it is imperative that we understand the molecular and cellular mechanisms that contribute to the homeostasis of the glomerular filtration barrier in order to devise new and more efficient tools to halt the progression of glomerulosclerosis and ideally prevent glomerular disease.

Although multiple factors contribute to the initiation and progression to glomerulosclerosis [1], in this review we will focus on the interactions between glomerular cells with the surrounding ECM, as these interactions play a critical role in regulating the response of the glomerulus to injury and progression to glomerulosclerosis. We will briefly describe the major matrix components, namely collagens and laminins, found in the adult glomerulus and how changes in their expression contribute to glomerular injury. We will then describe the role of three major matrix receptors, namely integrins, discoidin domain receptors (DDR), and dystroglycan in the control of glomerular homeostasis in healthy and diseased glomeruli. Finally, we will discuss the hope and tribulations of targeting these receptors for the treatment of glomerulosclerosis.

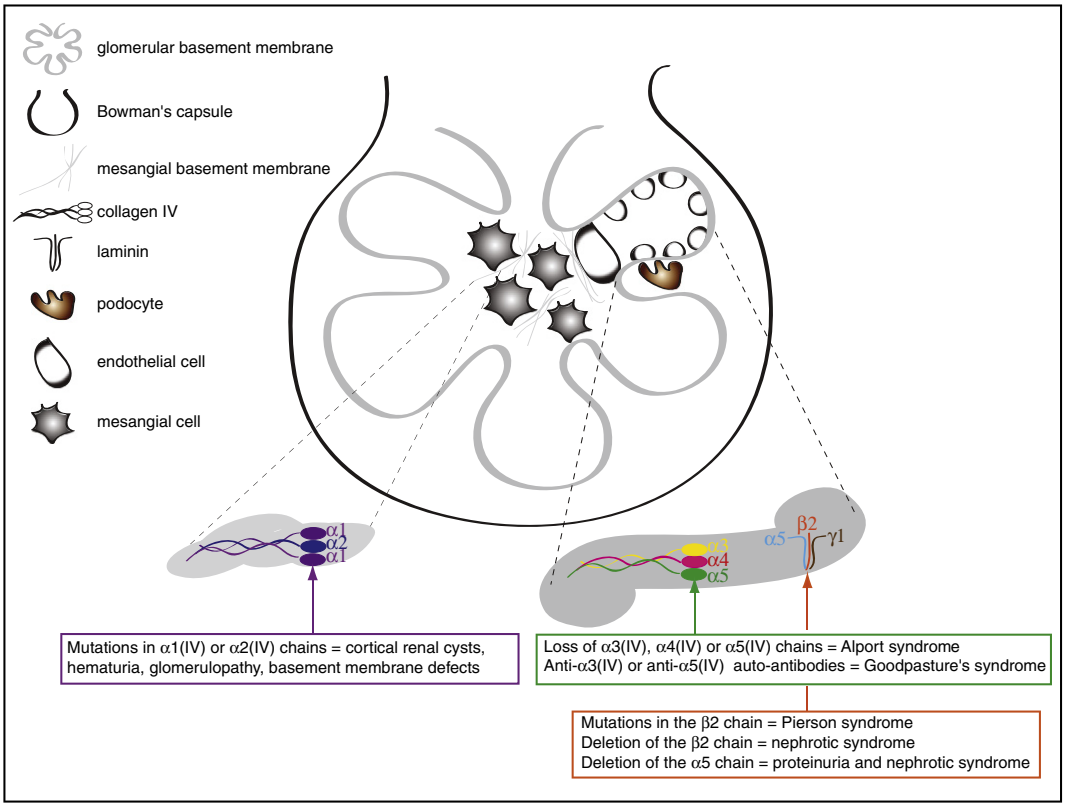

Fig. 1 – Schematic representation of a glomerulus highlighting the three major cell components and the two major basement membranes. Diseases or glomerular phenotypes associated to loss of collagen IV chains (in both mesangial and GBMs), or laminin-521 (in the GBM) are highlighted. See text for details.