PLASTICITY OF MESANGIAL CELLS: A BASIS FOR UNDERSTANDING PATHOLOGICAL ALTERATIONS

G. A. Herrera, M.D.
Department of Pathology
Louisiana State University Health Sciences Center, Shreveport, LA

The glomerular mesangial cells were first recognized as a distinct cell type by Zimmermann in 1933. Mesangial cells constitute approximately 30-40% of the total glomerular cell population. These mesangial cells spread from the hilum of the glomerulus in an arboreal pattern and are embedded in their own extracellular matrix. These cells have direct continuity and maintain close contact with cells that populate the juxtaglomerular apparatus. The mesangium is responsible for providing support to the entire glomerular structure and maintaining the glomerular capillaries open.

In a seminal paper exquisitely written and illustrated by Marilyn Farquhar and George E. Palade titled: “Functional evidence for the existence of a third cell type in the renal glomerulus” published in 1962, the authors provided for the first time evidence that the so-called deep cells of the glomerulus-mesangial cells- exhibited distinct morphological and functional characteristics that separated them from endothelial and epithelial glomerular cells. At the time the existence of this third type of glomerular cells was still being disputed and quite controversial. The authors went on to speculate that on the basis of the location of these cells and by virtue of their occasional phagocytic activity, the mesangial cells likely participated in the disposal and degradation of filtration residues and noted that these cells closely resembled capillary pericytes. It was pointed out that these morphological and functional characteristics clearly separated mesangial cells from other glomerular cell types. More than 40 years later the hypotheses of Farquhar and Palade have been proven to be absolutely correct and although our understanding of mesangial cells is far more complete we are still adding crucial information to the role that these cells play in health and disease.

The glomerular mesangium consists of resident mesangial cells and extracellular matrix. Two types of mesangial cells: a predominant smooth muscle-like cell with myofilaments and contractile properties and a second much less common phagocytic cell type (only about 3-10% of all mesangial cells) have been documented to be present in the normal mesangium. Morphologically the first type of mesangial cells show branching cytoplasmic processes with well developed filamentous network rich in actin and attachment plaques. The second mesangial cell type was felt to be derived from the bone marrow and has been shown to express Fc and C3 receptors. The normal mesangial matrix contains predominantly collagen IV but also has other extracellular matrix glycoproteins such as laminin and fibronectin, as well as proteoglycans including biglycan and decorin. Ultrastructurally, the mesangial matrix is seen to contain a dense network of microfibrils, which serve to anchor the mesangial cells. Mesangial cell functions are many and include regulation of capillary flow, maintenance of glomerular structure, production of vasoactive substances, cytokines and matrix components. Normal mesangial turnover is the result of a tightly controlled and dynamic equilibrium between the synthesis of new matrix and degradation and removal of the “old” matrix.
There are a number of key players that maintain equilibrium in the mesangial matrix in normal conditions. In essence, mesangial homeostasis is maintained by a balance of extracellular matrix production stimulated by transforming growth factor (TGF)-β and matrix destruction primarily resulting from activation of matrix metalloproteinases (MMPs) which are themselves maintained under control by tissue inhibitors of metalloproteinases (TIMPs), plasminogen activator inhibitor (PAI) and other non-specific inhibitors such as alpha-2 macroglobulin. Furthermore, changes in the amount and composition of the mesangial matrix can be associated with profound effects on the ability of mesangial cells to function properly. Any changes in these regulatory molecules leads to alterations in mesangial homeostasis and morphological expressions of disease that we use as diagnostic criteria. Thus, an appreciation of the mechanisms that determine the amount and composition of the mesangial matrix is of paramount importance to understand normal glomerular function and the results emanating from pathological changes.

One of the hallmarks of a great number of glomerulonephritis is the proliferation and activation of mesangial cells. Receptors have been described in mesangial cells that interact with a variety of stimuli and injurious agents leading to cellular alterations and if uncontrolled to pathologic results. Platelet-derived growth factor (PDGF)-beta (β) activation results in mesangial cell proliferation. Interestingly, TGF-β, the mesangial cell matrix rebuilder, is an anti-mitogenic factor for mesangial cells. Mesangial cells are very active metabolically synthesizing an array of substances such as cytokines which result in stimulation of cellular proliferation, cell shape changes, recruitment of inflammatory cells, including macrophages and monocytes, among many others. The interactions between cytokines and mesangial cells result in many of the alterations of the mesangial matrix that occur during the progression of immune and non-immune complex mediated glomerulopathies. Both resident and non-resident cells, including inflammatory cells, secrete factors that stimulate mesangial cell proliferation and matrix production, alter glomerular basement membrane permeability, and regulate blood flow. The native mesangial matrix is altered by the deposition of increasing quantities of normally expressed mesangial matrix components as well as other extracellular matrix proteins, which are not normally present in the mesangium. The mesangial matrix once initially altered, engages in a pathologic cycle which enhances further mesangial matrix expansion and further departure in composition from normal. If the pathologic process is not controlled, glomerulosclerosis occurs, resulting in a markedly altered mesangium morphologically and biochemically which is impossible to extremely difficult to repair and return to normal. Mesangial cells “trans” or “de” differentiate in response to injury. El Nahas refers to a change from the pericyte (smooth muscle) phenotype (“mesangiocyte”) to the embryonic myofibroblastic phenotype (“mesangioblast) as a characteristic response to mesangial injury. In the process, the mesangial cells acquire a range of cytoskeletal proteins, including alpha-smooth muscle actin. This process has been considered to reflect reverse embryogenesis of adult and mature mesangial cells. Change to the myofibroblastic phenotype eventually results in corresponding alterations in the mesangial matrix. These mesangial cells with myofibroblastic phenotype synthesize an array of different extracellular matrix proteins not normally present in the mesangium and difficult to destroy, including collagens I and III (interstitial/fibrillary collagens). The switch by mesangial cells from the production of collagen IV to
interstitial, fibrillary type of collagens has major pathologic consequences and represents a major factor in progression to glomerulosclerosis, as the glomeruli lack the necessary machinery (i.e. MMPs) to degrade the newly synthesized abnormal matrix components. Recent evidence supports that mesangial cells transform from the normal smooth muscle-like phenotype to a macrophage phenotype when exposed to certain injurious agents and engage in active phagocytosis. The plasticity of mesangial cells is responsible for glomerular damage, including mesangial matrix replacement, scarring and remodeling.

This presentation will discuss the importance of mesangial cells and matrix in maintaining normal glomerular structure and function (homeostasis) and also will address how the plasticity of these cells influences pathological glomerular events, repair and scarring. Our much more sophisticated understanding of mesangial cell behavior and mesangial matrix biology provides very useful information to help the design of new therapeutic approaches to the treatment of renal diseases. The potential for bone marrow-derived cells to differentiate into glomerular mesangial cells and repopulate damaged mesangium represents an exiting area of research that may lead to novel therapeutic strategies to address irreversible glomerular damage.
References: