

## Mesangial cells: renal function protagonists or coadjuvants?

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"THE PATH TO UNDERSTANDING FINDS RESISTANCE IN THE ORGANIZATION OF RESEARCH TOOLS."

PROF OMAR DA ROSA SANTOS

In order to achieve homeostasis, each kidney has about one million nephrons made up of different types of cells and tissues. The functional harmony of the cells of the renal parenchyma relies on a sophisticated bio-automation network devised to ensure the order and effectiveness of integrated biological responses. Mesangial cells (MC) and the mesangial matrix were first described in the mid-nineteenth century, as the components of a region called glomerular mesangium (between vessels). For a long time mesangial cells were analyzed by optical microscopy and considered merely as histological structures developed to provide axial support for capillary loops within the glomeruli. In 1951, Homer Smith<sup>1</sup> referred to mesangial cells as "a rare third cell type present in the glomerulus, located in the intercapillary axial structure". In light of current research tools, mesangial cells are seen as a special form of microvascular pericytes, which combine to form a mesangium/endothelium/epithelium functional integration unit. Strategically located, mesangial cells are directly involved in biological phenomena governing renal physiology and embryology. In this triply integrated circuit, changes occurring in one cell type can produce corresponding effects in others. The interactions result in "cross-talking" modulated by signaling pathways which include gap junctions, hormones, cytokines and

chemokines.<sup>2</sup> MC contractile properties allow them to participate in the control of intraglomerular capillary blood flow, glomerular ultrafiltration area and, consequently, individual nephron glomerular filtration rates (Figure 1). Mesangial cells produce structural components of the glomeruli, vasoactive agents, growth factors, cytokines, chemokines, erythropoietin, and elements of the complement system.<sup>2</sup> In terms of paracrine effects, mesangial cells express receptors for different vasoactive agents, growth factors, adhesion molecules, chemokines, and cytokines, among others. This set of factors physiologically assigns mesangial cells roles in functional regulation and remodeling of renal tissue.

Modern research tools have yielded a significant number of *in vitro* and *in vivo* experiments which revealed the active role of mesangial cells in different pathophysiological processes affecting the nephrons. One of the most relevant is the relationship between MC proliferation and the subsequent development of the mesangial matrix, observed in immune and non-immune glomerular injuries, particularly the pathophysiology of diabetic nephropathy.<sup>3</sup> Closer analysis of the glomeruli has shown that mesangial cells are not completely homogeneous. As many as 10% of them have different phenotypes when compared to other mesangial cells, in addition to presenting phagocytic behavior, expressing surface markers and cytokines found only in immune system cells, for which reason they were named myeloid dendritic cells.<sup>4</sup> Mesangial cells also

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**Figure 1.** Ludic Physiology: *Turnera ulmifolia* L. The flower opens and closes around its axis, according to the circadian rhythm and biological mediators. Are these biological mediators specific? As an illustration, the glomeruli partially mimic these movements of contraction and expansion, obeying biological mediators operating in the mesangium. Since the Aztecs, the active principles in this plant have been used in folk medicine. They have been said to work as anti-inflammatory agents, tranquilizers, and antidepressants, in addition to being used to treat impotence, diabetes, albuminuria, acne and tumors. Recently, they have been proven to work as an antibiotic against methicillin-resistant *Staphylococcus aureus* (MRSA), and *Trichophyton*, *Microsporium*, and *Epidermophyton* fungi.



express toll-like receptors<sup>5</sup> (TLR) TLR-1, 2, 4, 5 and 6 (which recognize bacterial surface antigens) and TLR-3 (which recognizes viral RNA), showing how close the innate immune system is to mesangial cells, as they play a role as triggers for inflammatory response and sites for interaction with immune complexes in the event of renal injury and systemic disease. Mesangial cells also impact the proliferation of kidney cells, as they produce both mitogenic (IL-6) and pro-apoptotic (TNF) cytokines.

Molecular research tools were instrumental in the advancement of knowledge on nephrology. In the realm of the molecules involved in renal physiology and pathophysiology, angiotensin II (Ang II) occupies a special place. Ang II is a peptide with dose-dependent effect triggered through tissue receptors located in the kidney and systemic tissues. Since the late 1980s, Ang II has been directly implicated in the development of glomerular

sclerosis by inducing the synthesis and secretion of transforming growth factor  $\beta$ . In the mesangium, in addition to contractile effects, Ang II also induces MC hypertrophy and interferes with the architectural structure of glomeruli and kidneys. Razvickas *et al.*<sup>6</sup> have significantly contributed to the development of knowledge on the pathophysiology of mesangial cells submitted to hypoxia and reoxygenation (H/R). Using an *in vitro* experimental model with immortalized mesangial cells, the authors reported increased intracellular basal  $[Ca^{2+}]$  and decreased cell reactivity to Ang II after H/R, both mediated by nitric oxide and not prostaglandins or potassium channels. Although obtained under artificial conditions, the study's results may potentially shed light on the pathophysiological phenomena triggered by H/R in the *in vivo* renal parenchyma. These observations were also relevant to understand the effects of H/R on the regulatory mesangium-endothelium-epithelium axis. The analysis of cell events occurring during acute kidney injury by hypoxia is no longer limited exclusively to the tubular epithelium, but extends throughout the nephron.

Mesangial cells have transitioned from a supporting into a leading role in the analysis of renal function of healthy individuals and patients with disease. Do not be surprised to see them become the therapeutic target of choice for a generation of new drugs designed to treat renal parenchymal disease.

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