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Physiology and pathophysiology of the mesangial cell

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The intercapillary area of the kidney glomerulus was first described and named «mesangium» by Zimmermann in 1933 [1]. The advent of electron microscopy enabled Marinozzi in Italy [2] and Latta in the U.S. [3] to conclusively demonstrate that a separate cell type exists in the kidney glomerulus, in addition to epithelial and endothelial cells lining around the basement membrane. The functions of these «mesangial» cells have been subsequently elucidated, based on recognition of their contractile phenotype and involvement in a variety of glomerular diseases (table I) [4-7].

Mechanical / structural functions

Mesangial cells are relatively rare in a normal glomerulus, not exceeding 2-3 nuclei in a typical light microscopy section of a mesangial space. Their total number is approximately 250-300 in a rat glomerulus [8]. Scarce extracellular matrix surrounds mesangial cells and bridges the space between neighbouring podocytes and endothelial cells. A direct relationship exists with the glomerular basement membrane at specialized structures termed «mesangial angles» by Kriz and Sakai [9]. These links may serve a mechanical function, exerting traction on the basement membrane so to counterbalance the hydraulic force driving ultrafiltration [10].

The smooth muscle phenotype in vivo, and the ability of cultured mesangial cells to undergo contraction when exposed to vasonstrictors, and relax in response to vasodilators, has attracted interest around the possibility that these cells may regulate the caliber of glomerular capillaries, and thus blood pressure and flow, with obvious implications on ultrafiltration [4-7, 11]. While conclusive in vivo evidence is difficult to achieve, many ex vivo or in vitro findings suggest that this may well be the case. First, the volume of glomeruli varies in response to contractile agents, indicating that responsive smooth muscle elements reside within the capillary tuft [4-10]. As mesangial cells are abundantly endowed with actin and myosin bundles, they are major candidates for this mechanical function. Additionally, contractility in culture, regulated by a variety of vasoactive agents [5], is consistent with such model. Second, the single nephron glomerular filtration rate is a function of two determinants: the mean net ultrafiltration pressure, resulting from the balance between hydraulic and oncotic pressures across the filtering unit, and the ultrafiltration coefficient, K_f. This parameter has been ex-

Table I. Recognized functions of glomerular mesangial cells

1. *Mechanical - structural*
   - — Perivascular, intercapillary cell (pericyte)
   - — GBM tensioning, countering P_{uf}
   - — Contraction / regulation of filtration surface area
   - — Matrix elaboration, processing
   - — Reparative proliferation following immune injury
2. *Ultrafiltration*
   - — GBM-like filtration of plasma
   - — Sieving of macromolecules, immune complexes
3. *Immune-effector cell*
   - — Antigen presenting
   - — Phagocytosis
   - — Reactive oxygen species production / scavenging
   - — Leukocyte chemoattraction
4. *Biosynthesis*
   - — Bioactive lipids
   - — Enzymes
   - — Matrix components
   - — Cytokines
   - — Growth factors
   - — Adhesion molecules

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perimentally found to vary in several pathophysiologic settings. Interestingly, both its determinants, the surface area (A) of capillaries and the effective hydraulic permeability of the glomerular capillary wall (k), are likely to change as the result of mesangial contraction [12]. Third, selective experimental mesangial injury by specific antisera often results in impairment of glomerular flow and filtration, that would be difficult to explain if mesangial cells had no role in glomerular hemodynamics [5, 6, 11].

Contraction is not the only mechanical function subserved by mesangial cells. Deposition of extracellular matrix is another prominent feature with likely implications for glomerular function. Not only does matrix contribute to the normal architecture of the mesangial space, but it also constitutes a tridimensional meshwork that allows filtration of blood, similar to the glomerular basement membrane (GBM) [4-7]. As a matter of fact, the biochemical composition of the mesangial matrix resembles that of the GBM, while its spatial organization seems better suited to trapping of macromolecules and immune complexes, which are then disposed of through phagocytosis and subsequent progression across the mesangial space [13].

Upregulation of mesangial matrix is an interesting feature of several glomerular diseases. This event may result from increased deposition of matrix, reduced catabolism, or possibly the combination of both [14]. A number of growth factors and cytokines, both released by glomerular cells and infiltrating leukocytes, appear well suited to stimulate matrix accumulation. This event seems to underlie glomerular lesions in slow-progressing, non-inflammatory conditions, such as diabetes or focal glomerulosclerosis. The occurrence of mesangial hyperplasia, or proliferation of the cells, whose number is actually increased, is often encountered in more rapidly evolving diseases, with extensive leukocyte infiltration, necrotizinglesions, and the signs of acute or subacute inflammation. These are features of mesangiocapillary nephritis, lupus nephritis, rapidly progressive glomerulonephritis, or vasculitis. Clearly, the pathophysiologic mechanism of mesangial involvement is different, although the common denominator seems represented by in situ cell «activation» with phenotypic changes. This has brought interest into the functional connotations of mesangial cells, which appear rather poorly differentiated under resting conditions in the normal kidney. Latta coined the expression «myofibroblast» to describe this wide potential of mesangial cells to express a contractile or secretory / reparative phenotype, according to the functional needs and the presence of appropriate stimuli [4, 11]. Indeed, recent evidence that smooth muscle actin isoforms are expressed by mesangial cells upon induction of immune-mediated damage points to the availability of «markers» of mesangial activation in vivo [11].

Immunologic functions

The presence of specialized phagocytes within the glomerular mesangium has long been a matter of controversy. The mesangial population is mostly accounted for by a smooth muscle / fibroblastic phenotype that seems only marginally suited for immune functions as either antigen-presenting cells or «professional» phagocytes [4-7]. Only 2 to 5 % of the cells confined in mesangial areas display obvious markers of bone marrow origin, such as the leukocyte common antigen or the Ia marker of phagocytic differentiation [15, 16]. Interestingly, bone marrow suppressive treatment rapidly depletes the glomerulus of these cells, clearly showing that they

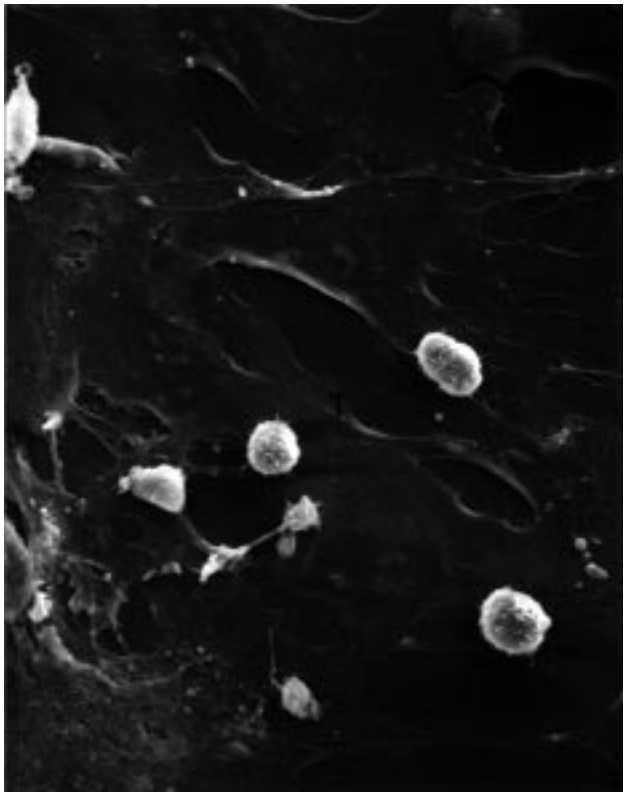

Fig. 1.—Binding of undifferentiated human myelomonocytes of the U-937 cell line to cultured human mesangial cells. Note tight adhesion of monocytes to underlying mesangial cells via cytoplasmic processes. Scanning electron microscopy, original magnification 1000 ×.

migrate into the mesangium from the blood stream and differentiate in situ, most likely to serve phagocytic functions [16]. Culture of glomerular explants gives rise to a homogeneous cell population devoid of such markers, that should be considered as «intrinsic» mesangial cells. Nevertheless, evidence has been gathered showing that these cultures indeed internalize and process opsonized gold particles, latex-coated microbeads, and immune complexes [17]. The process appears to involve Fc receptors, whose cross-linking appears to elicit specific biochemical events such as phosphoinositide breakdown, changes of free cytosolic Ca^{2+} ($[Ca^{2+}]_i$), and prostaglandin (PG) biosynthesis [18, 19]. The release and scavenging of reactive oxygen species, not only as a byproduct of normal cellular metabolism, but also in response to specific immunologic challenge, further points to an active participation in the immune response [20]. This may account for the accumulation of immune complexes in mesangial areas occurring in various experimental and human nephritides, as a result of trapping through the reticular structure of the mesangial matrix, and delayed or insufficient clearance of the deposits [21]. Failure of the mesangium to rapidly dispose of the material accumulated during filtration or formed in situ may explain this common finding, probably responsible for triggering subsequent glomerular inflammation and leukocyte chemoattraction [21].

Recent work has elucidated the mechanisms by which mesangial cells represent a target for neutrophils or monocytes / macrophages that infiltrate the glomerulus [22, 23]. Mesangial cells express a variety of integrins and adhesion molecules that promote leukocyte chemoattraction and adhesion (figure 1). While devoid of endothelial integrins such as ELAM-1, mesangial cells express intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), RANTES and monocyte chemoattractant protein-1 (MCP-1), all of which appear upregulated by several cytokines and ligands released at the site of inflammation [23-28]. Together with matrix components that bind leukocyte counterreceptors, this sets the stage for further leukocyte infiltration and local activation, thus perpetuating glomerular inflammation [22]. The role of vasoactive agents such as constrictor prostaglandins (PG), leukotrienes (LT), platelet activating factor (PAF) and even the endothelial products endothelin-1 (ET-1) and angiotensin II (ANG II) remains to be elucidated. As discussed earlier, these compounds may modify the mesangial phenotype and promote expression of surface determinants that trigger homing of leukocytes and amplify local damage. Local hemodynamics itself, controlled by such vasoactive agents, may indeed be relevant to glomerular inflammation.

Biosynthetic functions

Mesangial cells have secretory features beyond biosynthesis and layering of extracellular matrix. Both in vitro and in vivo, there is extensive evidence that bioactive lipids, such as arachidonate metabolites or PAF, enzymes, vasoactive peptides, and cytokines are locally produced and released. Interestingly, mesangial cells generally express receptors for all of these compounds, pointing to autocrine effects or paracrine interactions with contiguous mesangial cells, glomerular epithelial and endothelial cells, and possibly infiltrating leukocytes during glomerular inflammation. Table II lists the major products of mesangial cells presently identified.

Bioactive lipids are generally labile derivatives of plasma membrane turnover, released as means of intercellular communication upon stimulation of membrane-associated phospholipases. Endowed with powerful vasomotor activity, PG, LT and PAF have other cellular actions that include regulation of proliferation and protein synthesis, leukocyte chemoattraction, and probably vascular permeability [29].

Table II. Major products of glomerular mesangial cells

Growth factors
Platelet-derived growth factor
Transforming growth factor - ß1
Insulinlike growth factor 1
Cytokines
Interleukins 1, 6, 8
Tumor necrosis factor
GM - colony stimulating factor
Adhesion molecules, chemokines
ICAM-1
VCAM-I
MCP-1
RANTES
Bioactive lipids
Prostaglandins, leukotrienes, lipoxins
Platelet activating factor
Vasoactive agents
Endothelin-1
Nitric oxide (EDRF)
Enzymes
Renin
Neutral proteinases

Renin has been one of the first enzymes identified in mesangial cultures [30, 31]. The patterns of renin regulation match those described for juxtaglomerular cells, suggesting structural similarities between cell populations that may be electromechanically coupled via a syncytial organization [32]. Interestingly, cultured cells retain this ability to form syncytial structures, that have been recently exploited by means of diffusible tracers and microinjection [33].

The significance of renin biosynthesis may be better appreciated if one realizes that components of the renin-angiotensin system, including converting enzyme activity in glomerular endothelial cells, may locally function to generate active ANG II in situ, within the glomerular microcirculation. Since abundant receptors exist for this peptide both in mesangial cells, afferent and efferent arterioles, as well as glomerular epi- thelial cells, ANG II is well suited for autocrine or paracrine regulation of local hemodynamics, along with cell growth and matrix formation [5, 6, 12, 34].

Another peptide relevant to the control of vascular tone, ET-1, has been recently identified as a product of mesangial cells [35, 36]. Similar to the renin-angiotensin system, it is likely that local loops link the biosynthesis of ET-1 by mesangial and neighbouring endothelial cells to mesangial receptors, with implications for a wide range of pathophysiological events. Both populations also exhibit nitric oxide synthetase activity [37, 38]. As the constitutive and inducible isoforms of this enzyme release the potent vasodilator, nitric oxide, or endothelial-derived relaxing factor (EDRF), an endothelial - smooth muscle feedback has been proposed, with two opposite branches regulating the vascular tone of the glomerular capillary microcirculation.

Cytokines are another relevant product of mesangial cells. Several interleukins, notably IL-1 and IL-6, are produced by «activated» cells, and act on receptors expressed by the same cells [39-42]. γ-Interferon, GM-CSF, tumor necrosis factor, MCP-1, RANTES [26, 27, 43, 44] are other examples of the wide host of mesangial peptides acting on bone marrow-derived cells that also appear to mediate paracrine interactions within the inflammed glomerulus. Adhesion molecules belonging to the integrin superfamily regulate adhesion and cell-to-cell immune reactions [22]. Platelet-derived growth factor (PDGF) isoform AA is the predominant growth factor produced by mesangial cells [45, 46], although relevant levels of transforming growth factor-1 (TGF-ß) [47], insulinlike growth factor 1 (IGF-I) [48], fibroblast growth factor (FGF), epidermal growth factor (EGF) [46] have been reported. Interestingly, PDGF gene expression appears an early step in the response of mesangial cells to several mitogens, such as thrombin, ET-1, etc. [49]. The biological significance of this reponse is unclear, as mesangial cells express mostly ß isoforms of the receptor for PDGF, which are known to bind the homodimer BB or the heterodimer AB, but not the endogenous form AA [49]. The endogenous peptide is thus likely to act at sites other than the intrinsic mesangial cells, since its role in the early phase of mesangial proliferative glomerulonephritides has been convincingly shown [50]. A vast body of studies employing blocking anti-TGF-ß1 antibodies or binding glycans implicates also this growth factor in a variety of glomerular diseases with predominant mesangial expression [51-53]. A unifying view combines the two growth factors as sequential activators and regulators of mesangial proliferation and matrix deposition [11].

Conclusions

The vast number of publications focusing on mesangial cells testifies to the extreme interest raised in recent years by this apparently amorphous and inert structure of the glomerulus. The search for a key player in the reshaping of the filtering unit that occurs following immunologic or metabolic insult, has placed high hopes on the possibility of understanding and manipulating mesangial cell function. It is unclear whether these expectations will be eventually met, introducing pharmacologic means to arrest the relentless progression of glomerular scarring that characterizes so many renal diseases. In any circumstance, the contribution of cell culture and molecular biology will be certainly acknowledged as a major effort in the understanding of renal function in health and disease.

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