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Mesangial pathology in glomerular disease: targets for therapeutic intervention ☆

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ABSTRACT

The glomerulus is the filtration unit of the kidney. Disruption of glomerular function may be caused by primary glomerular pathology or secondary to systemic diseases. The mesangial, endothelial and epithelial cells of the glomerulus are involved in most pathologic processes. Animal models provide an understanding of the molecular basis of glomerular disease. These studies show that mesangial cells are critical players in the initiation and progression of disease. Therefore, modulation of mesangial cell responses offers a novel therapeutic approach. The complex architecture of the kidney, specifically the renal glomerulus, makes targeted drug delivery especially challenging. Targeted delivery of therapeutic agents reduces dose of administration and minimises unwanted side effects caused by toxicity to other tissues. The currently available modalities demonstrating the feasibility of mesangial cell targeting are discussed.

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Systemic administration of anti-inflammatory agents has been the primary focus for the treatment of glomerular diseases. Recent studies by us and others suggest a critical role for glomerular cell responses in the progression of renal disease. Therefore, delivery of drugs to the renal glomeruli inhibiting local inflammatory/pathogenic responses will be expected to yield better therapeutic outcomes. Targeted therapies have shown to lower drug dosing and thereby minimise side effects. This is especially attractive in chronic renal diseases requiring treatment over extended periods. This article discusses the glomerular mesangial cell, its role in glomerular disease and some cellular pathways that are potential targets for therapy. Animal models demonstrating therapeutic potential and new strategies of mesangial targeting are discussed.

1. Mesangium, mesangial matrix and mesangial cells

The mesangium forms the central region of the renal glomerulus and provides support to the glomerular tuft [1,2]. It consists of mesangial cells (MCs) embedded in an extracellular matrix (ECM). The ECM is produced by MCs and contains collagens type IV and V, laminin A, B1

Abbreviations: MCs, mesangial cells; ECM, extracellular matrix; GN, glomerulonephritis; IL, Immunoliposomes.

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and B2, fibronectin, heparan sulphate and chondroitin sulphate proteoglycans, entactin and nidogen. The MCs constitute 30-40% of the total glomerular cell population [3]. Two different types of MCs have been described. Vascular smooth muscle-like cells containing smooth muscle actin and myosin form >90% of the MC population. Processes from these MCs connect to the glomerular basement membrane and the juxtaglomerular apparatus either directly or through the extracellular microfibrillar proteins. Contraction of MCs can constrict the capillary lumen causing alteration of blood flow into the glomerular tuft, influencing glomerular filtration [4]. A smaller population of bone marrow-derived major histocompatibility complex (MHC) II positive, macrophage-monocyte-like phagocytic cells has been described in rats and constitutes 3-10% of MCs. These cells are not seen in normal glomeruli in humans [5]. The mesangium is separated from the vascular compartment by a fenestrated endothelium without an intervening basement membrane (Fig. 1). Thus, MCs are housed in a unique environment that communicates between the vasculature and the interstitium. MCs are exposed to changes in glomerular blood flow, plasma components and macromolecules percolating through the endothelial fenestrae. In addition to maintaining the glomerular haemodynamics, MCs perform a large number of critical functions and have been reviewed extensively [1]. Of specific relevance to this review is the ability of MCs to clear circulating immune complexes, to produce pro-inflammatory mediators and to regulate the formation and breakdown of the mesangial matrix in glomerular disease.

2. Role of MCs in glomerular pathology

Glomerular diseases manifest as diverse clinical syndromes and aetiologies are not clearly understood. Glomerular changes are complex, involving all glomerular cell types including MCs, endothelial cells, podocytes, parietal epithelial cells and infiltrating inflammatory cells [2,6–9]. Deposition of immunoglobulins (Ig) or immune complexes in the mesangium is one of the causes of glomerular injury and is seen secondary to diseases such as systemic lupus erythematosus (SLE)[10] or primary diseases such as IgA nephropathy [11]. Immunoglobulin aggregates activate MCs by signalling through surface Fc receptors.

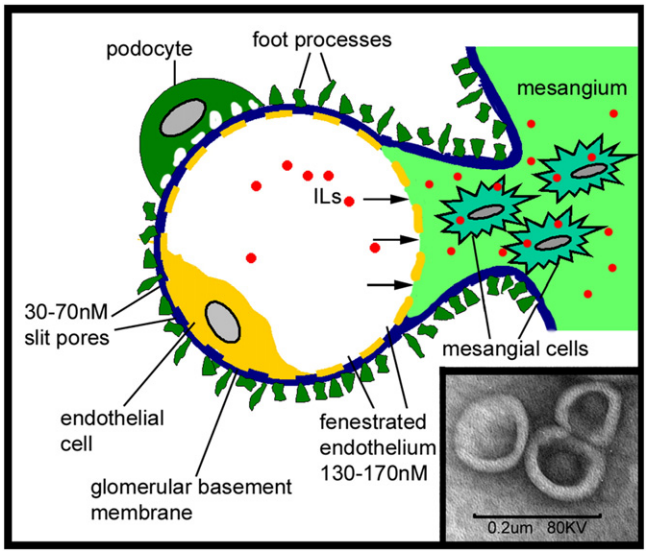

Fig. 1. Schematic of a glomerular capillary loop showing the glomerular filtration assembly with the capillary lumen surrounded by a fenestrated endothelium, glomerular basement membrane and podocyte foot processes. Note: Absence of basement membrane between mesangium and endothelium. Immunoliposomes (ILs) ~100 nM in diameter can traverse through the fenestrated endothelium directly into the mesangial space. Antibodies on ILs recognizing surface mesangial cell markers allow preferential retention as well as cellular uptake. **Inset**: Electron micrograph of sized liposomal preparation showing unilamellar vesicles. (This figure has been previously published in Scindia et al. Arthritis & Rheum 58 (2008) 3884–3891).

Mesangial changes seen following glomerular injury include production of chemo-attractants for inflammatory cells, proliferation of MCs and loss of mesangial matrix (mesangiolysis), followed by excessive production of ECM (mesangial expansion). The ease of obtaining primary MC cultures has allowed extensive investigation into responses of MCs in glomerular injury. *In vitro* cultures cannot replicate the interactions between MCs, ECM, endothelial cells and podocytes and the constantly changing haemodynamic state of the glomerulus, all of which influence MC responses. However, despite several differences, the MC cultures demonstrate significant similarities with the responses *in vivo* [12].

SLE is characterised by circulating autoantibodies to cytoplasmic and nuclear antigens. Renal involvement in SLE is associated with the deposition of IgG-containing immune complexes in the mesangium and along the glomerular basement membrane (GBM). These immune complexes may develop *in situ* by the reactivity of circulating autoantibodies to negatively charged nuclear antigens deposited in the GBM and mesangial matrix [13]. Another source of mesangial immune complexes in SLE is direct deposition of immune complexes formed in circulation. The progression of renal disease in SLE has been investigated in inbred mouse strains susceptible to fatal, lupus-like glomerulonephritis (GN).

In MRL lpr/lpr mice, a model of lupus-like GN, the onset of mesangial immune-complex deposition was associated with an increase in renal expression of the pro-inflammatory chemokines CCL2, monocyte chemoattractant protein (MCP-1) and CCL5 (RANTES) and chemokine receptors CCR2 and CCR5 [14]. The source of these chemokines was identified to be MCs. Thus, MCs are primary responders to glomerular immune injury in SLE. In New Zealand Mixed (NZM) 2328 mice, IgG immune complexes are first seen in the mesangial regions [15]. Compared to a normal glomerulus (Fig. 2(A)), there is an increase in mesangial size and cellularity (Fig. 2(B)) associated with inflammatory cells such as neutrophils, dendritic cells, macrophages and T cells in the glomerular and periglomerular regions. In female NZM2328 mice, this acute proliferative phase progresses to chronic GN (Fig. 2(C)). Glomerular sclerosis and fibrosis are prominent along with interstitial inflammation in the renal cortex. Lupus mesangioproliferative GN is associated with increased levels of pro-inflammatory cytokines such as interleukin (IL)1β, tumour necrosis factor (TNF)α, IL6 and granulocyte macrophage colony stimulating factor (GMCSF) in the kidney. A significant increase in transforming growth factor (TGF)β is seen with the onset of chronic change The production of TGFβ as a critical mediator of glomerular sclerosis and fibrosis is well established in the final common pathway of end-stage renal disease [16,17].

Immune-mediated glomerular injury is also seen in IgA nephropathy characterised by immunoglobulin A (IgA) deposits in the glomerular mesangium as the diagnostic feature. Although IgA nephropathy has a wide range of clinical presentations, the most common pathologic feature is glomerular hypercellularity [18]. Patients with the familial form of IgA nephropathy produce abnormally glycosylated IgA, which deposits in the mesangium as multimers or immune complexes [19]. Treatment of human mesangial cell lines with IgA from asymptomatic relatives of patients' shows enhanced binding to MCs inducing increased production of IL6, TNFα and MCP1 compared to relatives of sporadic IgA nephropathy patients [20]. Pro-inflammatory chemokines and cytokines secreted by MCs act as chemoattractants to recruit inflammatory cells into the glomerulus. In addition, chemokines also cause activation of the endothelial cells in the glomerular capillaries and up-regulation of adhesion molecules, further facilitating inflammation. In another study, atypically glycosylated IgA or serum IgA from patients could induce platelet activating factor in MCs that can act on podocytes and lead to loss of nephrin [21]. *In vivo*, this would be expected to compromise glomerular filtration.

An example of metabolic glomerular injury is seen in diabetes mellitus. Diabetic nephropathy is associated with the involvement of