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Review

# Mast cells in renal inflammation and fibrosis: Lessons learnt from animal studies☆

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ABSTRACT

Mast cells are hematopoietic cells involved in inflammation and immunity and have been recognized also as important effector cells in kidney inflammation. In humans, only a few mast cells reside in kidneys constitutively but in progressive renal diseases their numbers increase substantially representing an essential part of the interstitial infiltrate of inflammatory cells. Recent data obtained in experimental animal models have emphasized a complex role of these cells and the mediators they release as they have been shown both to promote, but also to protect from disease and fibrosis development. Sometimes conflicting results have been reported in similar models suggesting a very narrow window between these activities depending on the pathophysiological context. Interestingly in mice, mast cell or mast cell mediator specific actions became also apparent in the absence of significant mast cell kidney infiltration supporting systemic or regional actions via draining lymph nodes or kidney capsules. Many of their activities rely on the capacity of mast cells to release, in a timely controlled manner, a wide range of inflammatory mediators, which can promote anti-inflammatory actions and repair activities that contribute to healing, but in some circumstances or in case of inappropriate regulation may also promote kidney disease.



## 1. Introduction

Chronic kidney diseases (CKD) are complex inflammatory disorders, which represent a growing health problem linked in part to the ageing population and to the increased incidence of diabetes and hypertension (DuBose, 2007; Trivedi et al., 2002). Besides these prime causes, CKD can arise from many other insults that affect kidney structures such as the glomeruli, renal vessels, and the tubulo-interstitial compartment (Schlondorff, 2008) including for example genetic defects as in dominant polycystic kidney disease or acquired factors such as exposure to toxic agents (drugs, metal compounds, etc.), post-ischaemic (shock), infectious, or autoimmune injury. Independent of the initial cause, renal injury launches an inflammatory cascade initiating tissue repair promoting tissue regeneration and limiting fibrosis development. However, in case

*Abbreviations:* AKI, acute kidney injury; CKD, chronic kidney disease; GBM, glomerular basement membrane; GN, glomerulonephritis; MC, mast cell; mMCP4, mouse mast cell protease 4; NS, nephrotic syndrome; PAN, puromycin aminonucleoside-nephrosis; SCF, stem cell factor; SLE, systemic lupus erythematosus; Treg, regulatory T cell; UUO, unilateral ureteral obstruction.

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of ill-regulation or chronic stimulation the response may also lead to manifest renal glomerulosclerosis and tubulointerstitial fibrosis with the final consequence of end-stage renal disease attained when most of the nephrons, the functional units of filtration, have been destroyed (Fig. 1).

Data obtained from many laboratories have found that mast cells represent major components of the tubulointerstitial infiltrate in renal disease, supporting a pathophysiologic role of these cells (Blank et al., 2007; Eddy, 2001). Mast cells are a heterogeneous population of cells of myeloid origin. Their precursors exit the bone marrow and after a short passage in the circulation migrate into tissues where they fully differentiate under the influence of stem cell factor (SCF) (Galli et al., 2005). While in normal kidney mast cells are relatively scarce, their numbers increase strongly (between 10- and 60-fold) in various kidney diseases (Blank et al., 2007). One of the prime functions of these cells is to release a whole variety of inflammatory products (Blank and Rivera, 2004; Pelletier et al., 1998). These can be released from secretory granules in the cytoplasm or newly synthesized upon stimulation such as for example lipid compounds and cytokines/chemokines/growth factors. These mediators participate in a complex network of events impacting on local tissue responses, tissue remodelling, cell–cell interactions and immune responses that together shape the physiological or pathological response. Mast cell derived products may also have regional or systemic effects as evidenced by local mast cell activation for example in the skin, gut or other sites that can lead to systemic anaphylactic shock (Galli et al., 2008). Likewise, upon infection mast cells can either themselves or via released

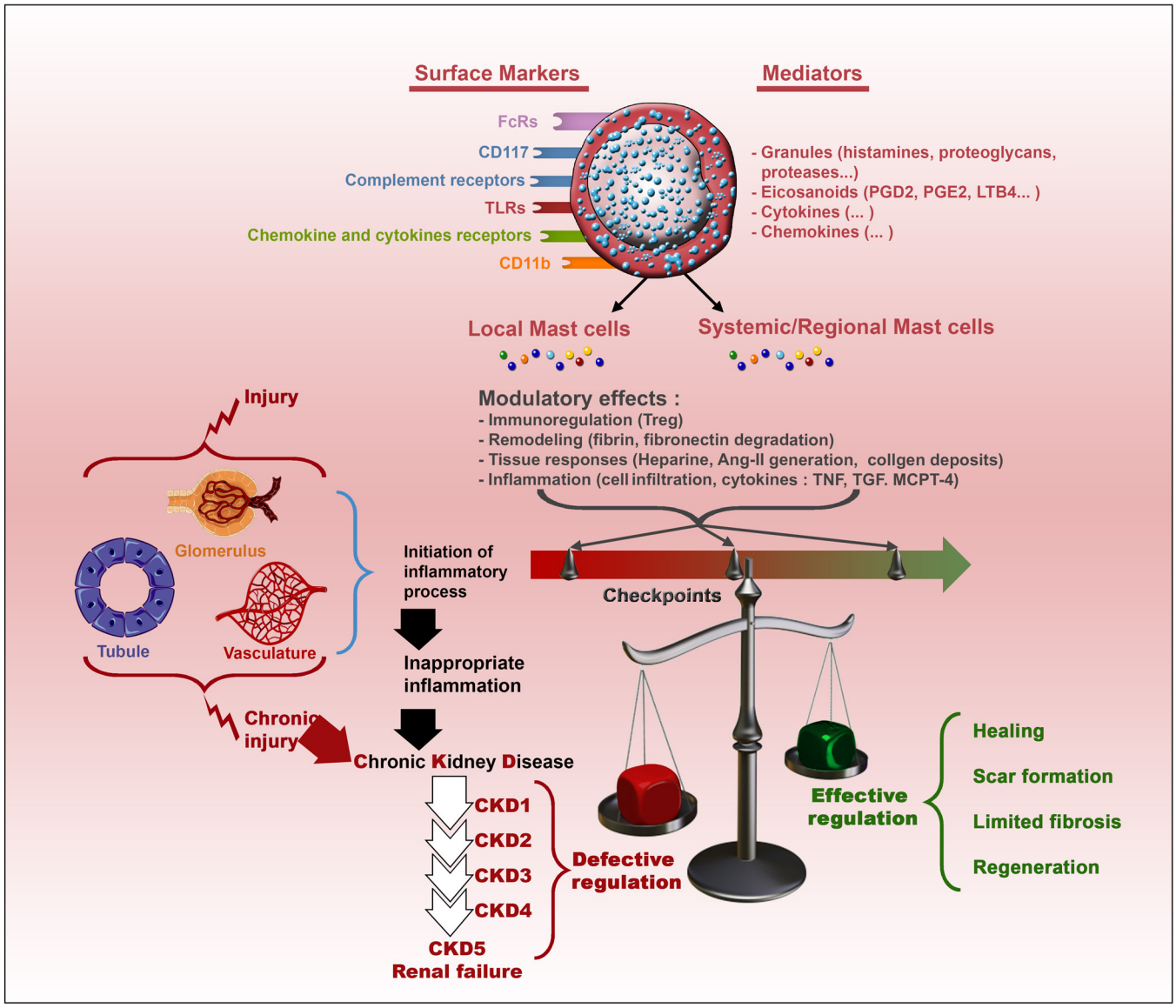


**Fig. 1.** The inflammatory process in renal disease. Renal disease gets initiated by an injury affecting either glomeruli, tubules or blood vessels. The ensuing inflammatory response is characterized by the release of inflammatory mediators from kidney resident or infiltrating cells, which will initiate immunoregulatory and inflammatory mechanisms, tissue responses and tissue remodelling. If well controlled and effectively regulated by positive and negative feed-back loops this will lead to healing, limited fibrosis development and in some occasions also regeneration of injured tissue injury. In case inflammation does not resolve because of a strong initial damage, chronic stimulation, or defective regulation, resident and infiltrating cells in the kidney interact will mediate disease progression entering the various stages of chronic kidney disease (CKD 1–5) CKD is characterized – depending on the initial insult – by the development of glomerulosclerosis, tubular atrophy and tubulointerstitial fibrosis with fibroblast proliferation and expansion of extracellular matrix thereby promoting nephron and vessel loss. There is significant redundancy of nephrons and typically 60–70% of them will have been destroyed before CKD is diagnosed, and from then on the damage progresses to end-stage renal failure (CKD5). Mast cells can participate in many steps of the inflammatory process, either after systemic activation or locally by secreting inflammatory mediators that may participate in the repair functions or, on the contrary, in kidney destruction and end-stage renal failure.