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Review

Mast cells and chronic kidney disease

Lislaine Andrade Wensing* and Niels Olsen Saraiva Câmara
Laboratory of Transplantation Immunobiology, Department of Immunology, Institute for Biomedical Sciences, University of São Paulo, São Paulo, Brazil

ABSTRACT

Mast cells (MC) are derived from CD34-positive multipotent bone marrow progenitor cells and they migrate to vascularized tissues where they complete their maturation and acquire a tissue-specific phenotype. Although present in small numbers in the normal kidney, MC accumulate in periglomerular and perivascular areas of the renal cortical tubulointerstitium in progressive nephropathies. The infiltration of MC was correlated with the degree of tubulointerstitial fibrosis and poor disease outcome, regardless of the underlying causes. Consequently, it was readily suggested that MC could contribute to the process of renal deterioration through the participation in tubulointerstitial fibrosis. Accordingly, once activated, MC secrete numerous vasoactive, pro-inflammatory and profibrotic mediators that have already been implicated in organ fibrosis. Therefore, MC targeting may represent a novel therapeutic approach to halt the progression of kidney fibrosis.

KEYWORDS: mast cell, inflammation, fibrosis, chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD) is the result of progressive loss of functional nephrons and manifests itself as glomerulosclerosis, vascular sclerosis and tubulointerstitial fibrosis. It is believed that tubulointerstitial fibrosis is the best predictor of decline in renal function and poor disease prognosis [1]. There is compelling evidence that inflammation plays a central role in the development of CKD, not only as an initiator of renal injury in immune-mediated nephropathies but also as propagators of tissue damage in other forms of nephropathies, often described as nonimmune. Tissue injury induces death or dysfunction of glomerular and tubulointerstitial cells stimulating local release of proinflammatory mediators including chemokines. These molecules attract inflammatory cells to the glomerulus or tubulointerstitium initiating a status of local inflammation, which leads to interactions between inflammatory cells and kidney resident cells. The non resolving inflammation after a sustained injury initiates the process of renal scarring by inducing the transformation of resident fibroblasts into myofibroblats, which are responsible for the synthesis and deposition of extracellular matrix (ECM) components. Thus, inflammation contributes to glomerulosclerosis and tubulointerstitial fibrosis, further reducing functional nephrons and thereby perpetuating the progression of CKD [2]. Among the immune cells that infiltrate the kidney after injury, lymphocytes and macrophages are the most studied; however, another kind of bone marrow (BM)-derived cell, MC, have also found their way to kidney [3].

MC are rarely found in the renal interstitium, however, accumulation of MC is prominent in kidney biopsies of patients with CKD, regardless of the underlying causes. Increased numbers of

*Corresponding author: Edifício Biomédicas IV, Departamento de Imunologia, Av. Prof. Lineu Prestes, Nº 1730. CEP 05508-900, Cidade Universitária São Paulo, SP, Brasil.
liswensing@gmail.com

MC were detected in the tubulointerstitium (periglomerular and perivascular areas) of renal cortical biopsies from patients with focal segmental glomerulosclerosis, membranous-proliferative glomerulonephritis, IgA nephropathy, lupus nephritis and diabetic nephropathy [4, 5, 6, 7, 8]. Furthermore, MC infiltration was shown to positively correlate with the degree of tubulointerstitial fibrosis and kidney function decline. Based on these observations, MC were readily implicated in the development of CKD. In this review, we discuss the recent advances in our understanding of the potential fibrogenic role of MC in the process of kidney scarring.

Mast cell biology

MC are long-lived resident cells located at the host's interfaces with the environment in areas such as skin, respiratory and gastrointestinal mucosa in association with blood vessels and nerve endings, near smooth muscle cells and mucus-producing glands. Due to their strategic location, MC are believed to be important agents of the body's primary defense against pathogens. These cells are derived from bone marrow CD34-positive multipotent progenitors and initiate their differentiation under the influence of stem cell factor (SCF) and IL-3 [9]. From the bloodstream, MC migrate to vascularized tissues where they complete their maturation and acquire a tissue-specific phenotype under the influence of the microenvironment [10].

Although traditionally known for their role in the allergic response, MC are currently considered important mediators and modulators of innate and adaptive immune response, chronic inflammation and immunological tolerance. These cells are also involved in the regulation of several homeostatic functions, such as coagulation and blood flow, smooth muscle contraction and intestine peristalsis, mucosal secretion and tissue remodeling [11, 12, 13].

The main mechanism of MC activation is though IgE-Fc cross-linking, which initiates a complex series of biochemical events, resulting in MC degranulation. However, MC can also be activated by bacterial or viral antigens, cytokines, growth factors, and hormones, leading to differential release of distinct mediators without degranulation [14]. Once activated, MC secrete numerous vasoactive and pro-inflammatory mediators. These include pre-formed molecules, such as histamine, serotonin, TNF-α, kinins and proteases stored in secretory granules. Leukotrienes, prostaglandins and platelet activated factor (PAF) are synthesized during MC activation from arachidonic acid released by the action of phospholipases. In addition, a number of cytokines (IL-1, 2, 5, 6, 8, 9, 13), chemokines (CCL-2, CCL-3, CCL-5 and CXCL8), growth factors (VEGF and TGF-β1) and metalloproteinases are newly synthesized and released several hours after stimulation [15, 16]. These diverse array of potent biologically active mediators account for the greater flexibility and diversity of MC responsiveness to meet the requirements of both physiological and pathological responses in which these cells may be involved.

Mast cell possible regulation of kidney inflammation

Inflammation is a frequent feature in all forms of kidney disease, irrespective of the primary causes. MC may contribute to initiation and regulation of tissue remodeling in response to kidney injury by stimulating local inflammation. Accumulating data indicate that MC are critical for the pathogenesis of inflammatory diseases [17]. In fact, it is now recognized that MC exert immunoregulatory functions such as recruitment, survival, development, maturation or function of immune cells. Thereby, MC are able to promote and control the magnitude and duration of the immune response. The recruitment of leukocytes from the mainstream of blood to the glomerulus or tubulointerstitium space is a key feature of the response to kidney damage. Interestingly, it was shown that MC influx to kidney precedes the infiltration of other effectors cells of the immune system such as macrophages and lymphocytes in hypertensive nephropathy [4]. Moreover, the recruitment of these cells was significantly reduced in the kidneys of MC-deficient mice submitted to the unilateral ureteral obstruction (UUO) model of renal tubulointerstitial lesion [18]. These observations indicate that MC may be responsible for the increased local production of mediators that lead to leukocyte recruitment to injured kidneys.

Chemokines are a group of specialized cytokines that act as potent mediators and regulators of inflammation due to their ability to recruit and activate leukocytes in allergic and other inflammatory conditions. They function as G protein-coupled chemotactic factors, which also activate the cells with which they interact. The receptors for chemokines are expressed in a cell type specific manner and are restricted primarily to subsets of leukocytes. Activation of MC causes transcription and translation of several different cytokines/chemokines such TNF-α, macrophage inflammatory protein-1 (MIP-1) GM-CSF, RANTES, CXCL8, CCL1, CCL2, CCL3, CCL4 and CXCL2 as well as the arachidonic acid metabolites prostaglandin D2 and leukotriene B4 (LTB4) [17, 19, 20, 21]. The requirement of MC for immune cell influx was shown in some models of infection or sterile inflammation in MC-deficient mice in which a significant reduction in leukocyte infiltration was observed [22, 23, 24, 25]. It was demonstrated that in the lungs of asthmatic individuals, lymphocyte recruitment was driven by elevated CCL1 levels produced by MC [26]. LTB4 production by MC following sensitization and challenge induces the migration of $CD8^+$ T cells into the lungs in a model of airway hyperresponsiveness [27]. Besides, MC also induce cell trafficking indirectly by inducing local release of chemoattractant molecules by resident or other infiltrating cells [28, 29]. Interestingly, it was shown that intrarenal mRNA expression of chemokine ligands, which are chemoattractants for monocytes (CCL5) and T cells (CXCL9, CXCL10, and CCL20) were decreased in MC-deficient mice in the UUO model [18].

MC also facilitate the influx of immune cells to the sites of inflammation by increasing endothelium permeability and the expression of adhesion molecules by vascular endothelial cells (EC) [30, 31]. Within tissues, MC are frequently found in perivascular localization. Consequently their released mediators can readily affect vasculature. The histamine stored in high concentrations in MC granules, is believed to be responsible for the most rapid actions of MC on the vasculature, acting through its receptors H1, strongly expressed on venular EC [32]. This molecule induces an increase in cytoplasmatic Ca^+ that results in the release of preformed products that microvascular EC store within their own granules, the Weibel-Palade bodies (WPBs) containing mediators that include Von Willebrand factor (vWF) and P-selectin, a cell adhesion molecule [33]. Tryptase, the major MC product is believed to elicit leukocyte rolling and adhesion through the protease receptor PAR-2 activation. Like histamine, PAR-2 activation results in exocytoses of WPBs by a calcium-dependent intracellular mechanism [34]. Another preformed molecule released upon MC degranulation, TNF-α, has rapid effects on EC by increasing permeability through cytoskeletal rearrangements [35]. In addition, TNF-α also induces the expression of adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), P-selectin, and E-selectin [36]. *De novo*-produced leukotrienes from arachidonic acid are potent vasoactive inflammatory mediators, which also elicit Ca^+ mobilization in EC, leading to secretion of vWF and P-selectin. Thus, MC facilitate leukocyte trafficking into the kidney through the release of pre-formed or newly synthesized mediators that control leukocyte rolling, adhesion, and transendothelial migration.

Finally, after having induced the influx of inflammatory cells, MC may promote the differentiation and function of these cells by numerous mechanisms such as release of cytokines, growth factors and proteases as well as by direct cell contact. It was reported that MC secretion of immunologically active exosomes induces B and T lymphocyte activation and secretion of cytokines [37]. It has been found that rat peritoneal MC can stimulate T cell proliferation through antigen presentation by either MHC class I- or class II-restricted mechanisms [38, 39] as well as T cell activation through cell-to-cell interactions between MC OX40L and T cell OX40 [40]. In addition, an apparent interdigitation of lymphocytes and MC membranes has been observed in inflamed allergic tissues [41]. MC can also modulate the function of lymphocytes indirectly through DC regulation [42]. Many MC mediators, like TNF-α, histamine, GM-CSF and some cytokines potentially influence migration, maturation and function of DC [43, 44]. These cells, in turn, functioning as potent antigen-

presenting cells, interact with T lymphocyte and control their Th1/Th2 balance [45]. With regard to macrophages, there is very little data showing the regulation of these cells by MC. One report showed that MC granules modulate alveolar macrophage respiratory-burst activity and eicosanoid metabolism [46]. It was also demonstrated that MC induced increase of low-density lipoprotein uptake by macrophages *in vitro* [47].

In conclusion, recruited and activated cells by MC are believed to promote further progression of the inflammatory response by providing additional sources of certain cytokines that may also be produced by MC, as well as new sources of cytokines and other mediators absent in MC.

Mast cell protease biologic activities and potential involvement in kidney fibrosis

MC proteases may account for more than 25% of their total protein content and some of them have mRNA levels similar or even surpassing those of housekeeping genes [48]. Therefore, upon MC degranulation, a very large amount of these proteases are released and probably they have a major impact on any condition in which MC activation occurs. Among the proteases expressed by MC, chymase and tryptase are of particular interest. Chymase and tryptase are endopeptidases selectively expressed by MC and stored in secretory granules tightly packaged in complexes with serglycin proteoglycan. These proteases are synthesized as inactive zymogens and are activated after autocatalytic intermolecular cleavage and/or proteolytic removal of a propeptide by dipeptidyl peptidase I [49, 50]. Thereafter they are stored in cytoplasmatic granules in their mature and enzymatically active forms, although restrained by the low pH of the granule that helps to prevent their autolysis [51]. Although being part of the same class of serine peptidases, chymase and tryptase differ in form, activity, substrate specificity and expression pattern. For example, chymases cleave substrates following aromatic amino acids, whereas tryptases cleave substrate C-terminal of basic amino acids. Additionally, their expression pattern divides MC in specific subsets. In rodents, MC are subdivided into connective tissue type mast cells (CTMC) and mucosal type mast cells (MMC). Murine CTMC express the chymases mMCP-4, mMCP-5, the tryptases mMCP-6 and mMCP-7 and carboxypeptidase (CPA3). In contrast, MMC express the chymases mMCP-1 and mMCP-2, but do not express tryptases or CPA3 [52]. In humans, MC are classified as either MC_T, which express tryptase only, or MC_{TC}, which express tryptase, chymase and CPA3 [15].

Besides their biologic action mediated by the cleavage of specific substrates, chymase and tryptase may also exert their function thought a receptor-mediated mechanism. It was demonstrated that these proteases are able to activate the protease-activated receptor-2 (PAR-2) [53, 54]. Protease-activated receptors (PAR) are a family of G protein-coupled receptors activated by cleavage of their extracellular NH2-terminal domain by proteolytic enzymes. The exposed NH2-terminal sequence acts as a tethered ligand that binds to a site on the second extracellular loop of the receptor, triggering its autoactivation and subsequent signaling cascade events, such as mitogen activated protein kinase (MAPK) pathways and calcium mobilization [55]. Consequently, MC release of its granule-stored proteases is directly converted into intracellular signals by way of PAR-2 activation.

PAR2 activation was shown to cause blood vessel relaxation, increased vascular permeability, leukocyte adhesion and release of pro-inflammatory cytokines [56]. Interestingly, it has been found that the kidney is an organ that is particularly rich in PAR-2 and also expresses other members of this receptor family (PARs 1 and 4). In the kidney, studies have detected PAR-2 expression in mesangial cells, blood vessel walls, interstitial fibroblastic cells, as well as tubular epithelial cells (TEC) [57]. PAR-2 expression was significantly increased, particularly in the proximal tubule of kidney biopsies from patients with IgA Nephropathy and was correlated with the extent of interstitial fibrosis [58]. More recently, MC infiltration was associated with the expression of PAR-2 and tubulointerstitial fibrosis in the same scenario [59]. In the UUO model, PAR-2 expression in proximal tubular cells (PTEC) was increased progressively starting from 24 h to the day 14 post-ligation [60]. Finally, PAR-2 activation *in vitro* was able to induce a significant

upregulation of TGF-β1 and PAI-1 gene expression in mesangial and TEC [58] as well as an increased expression of a range of inflammatory genes (TNF, IL-1β, GM-CSF and MMP-1) in human TEC. These reports suggest a potential role for MC-mediated PAR-2 activation in renal inflammation and fibrosis [61].

Chymase-dependent intrarrenal Ang II production

One of the mechanisms by which MC are supposed to promote kidney disease progression is via chymase-dependent Ang II formation [62]. In agreement, increased numbers of chymase-positive MC were observed in the kidneys of patients with different types of CKD and were correlated with the severity of interstitial fibrosis [6, 63, 64, 65]. Moreover, circulating chymase concentrations were increased in CKD patients while control subjects had undetectable plasma chymase concentrations [66].

Chymases are proteases with chymotripsin-like activity subdivided into two phylogenetic groups: α-chymases, widely expressed among different species and β-chymases, identified only in rodents. Humans express only α-type chymases and among the mouse chymases, MCP-4 is the only one with similar substrate specificity, tissue distribution and serglycin-binding properties. Thus, MPC-4 is considered the closest functional homolog to human chymase [67].

It was proposed that chymase-dependent Ang II formation would account for the so-called "angiotensin reactivation," characterized by the return of plasma Ang II concentration to pretreatment levels during chronic ACE inhibitor therapy [68, 69]. Moreover, this alternative pathway for generation of Ang II would explain why combined RAS blockade by ACE inhibitors and AT1R antagonist therapy is more effective than ACE inhibition alone in retarding the progression of renal insufficiency in CKD [70, 71]. Finally, chymase is the most likely candidate responsible for the maintenance of kidney, heart, and lung steady-state Ang II levels in genetic ACE deficiency [72]. Collectively, these data show the potential contribution of chymase-dependent intrarenal Ang II formation in the progression of renal injury. Accordingly, a reporting using specific pharmacologic inhibition of chymase has implicated the chymase-dependent Ang II formation to the pathogenesis of interstitial fibrosis in the UUO model [73]. It was also shown that chymase-deficiency (MCP-4 knockout) reduces inflammation and fibrosis in immune complex-mediated glomerulonephritis [74].

Activation of profibrotic factors by chymase

The potential profibrotic action of chymase goes beyond the Ang II-mediated intraglomerular hypertension and generation of growth promoting cytokines, free oxygen radicals and fibrosis mediators. This protease has also been shown to regulate TGF-β1 metabolism by promoting its latent form releasing from ECM [75] and activation by cleavage [76]. Thus, MC, through the production of chymase, activates two of the most well established mediators of renal fibrosis, Ang II and TGF-β1. Moreover, chymase has also been shown to convert Endothelin 1 (ET-1) precursor to its active form [77], thus being potentially involved in the Ang II-independent renovascular pathological changes mediated by this vasoactive factor [78]. It was also demonstrated that chymase, through PAR-2 activation, increased glomerular macromolecular permeability that leads to proteinuria and may initiate the glomerular damage. This effect was independent of alterations in hemodynamic factors or renal inflammation [79].

Nevertheless, opposing the evidences of the active role of chymase in the development of renal fibrosis, it was recently demonstrated that mice deficient in chymase, had enhanced fibrosis after UUO. In this report, chymase exerted a protective role due its capacity to degrade fibronectin, thereby diminishing adhesion of inflammatory cells in the tissue [80]. A protective action of chymase has already been shown in a model of spinal cord injury [81] and polymicrobial sepsis [82], in which chymase was believed to degrade inflammation-associated cytokines and thus limit inflammation. These contrary results indicate that chymase may exert detrimental or beneficial effects depending on the pathological scenario.

Tryptase regulation of fibroblast function

This trypsin-like serine protease accounts for up to 90% of the total protein content of MC

secretory granules [83]. Thus, MC degranulation will lead to the release of a large amount of tryptase, which may have a major contribution to MC function. Tryptase is stabilized as an enzymatically active tetramer by association with heparin, generating a conformational structure that restricts the access of macromolecular substrates and confers resistance to inactivation by endogenous proteases [84]. In humans, tryptases are subdivided into three groups: α-, β- and γ-tryptase [85, 86]. α-tryptase is the predominant form found in serum under normal conditions [87] whereas β-tryptases are the major type stored in MC secretory granules and are used as a specific indicator of MC activation [88, 89]. Mouse mast cell protease-6 (mMCP-6) is the major storage component of CTMC and its substrate preference resembles the human tryptases; hence, mMCP-6 is considered as the functional counterpart to human β-triptases [90].

Among the soluble substrates found to be cleaved by tryptase, some are inactivated, like fibrinogen [91], high-molecular-weight kininogen [92] and neuropeptides [93], whereas others are activated, as urokinase-type plasminogen activator [94] and matrix metalloproteinases 3 and 13 [95]. Interestingly, some of these proteins appear to be too large to fit into the central pore of tryptase tetramer. Active mMCP-6 monomers were detected in the presence of heparin oligosaccharides too small to induce their tetramerization. Differently from the tetramers, these monomers were able to cleave large substrates, e.g. fibronectin, and were susceptible to bovine pancreatic trypsin inhibitor [96]. This finding brings up the possibility that some of the reported activities of tryptase may actually be related to its active monomers.

It has been established that tryptase can directly alter cell behavior. For example, tryptase induces cell proliferation [30, 97, 98], secretion of pro-inflammatory mediators [30, 99] and production of ECM components [100, 101]. Activation of PAR-2 by tryptase was shown to be the main mechanism for its function, though it seems that the effect of tryptase on cells could also be elicited via a mechanism independent of PAR-2 activation [102]. Tryptase is the first protease other than trypsin that has been shown to activate this proteolytic receptor [103]. PAR-2 activation by tryptase leads to the activation of a variety of intracellular signaling cascades [104, 105, 106, 107]. Therefore, it is conceivable that tryptase may act primarily not to cleave substrates in the extracellular milieu, but rather to directly activate cells through PAR-2 or other receptors.

Accumulation of tryptase-positive MC is a common feature of renal interstitial injury. High concentrations of serum tryptase were observed in patients after kidney transplantation [108] or in patients with CKD caused by different nephropathies [109]. In this case, tryptase levels were positively correlated with markers of renal dysfunction. More than being an indicator of MC activation in the setting of kidney diseases, tryptase potentially has an active part in the process of tubulointerstitial fibrosis.

This protease has already been implicated to skin, lung and cardiac fibrosis [100, 110]. The main role of tryptase in tissue fibrosis is believed to be through the regulation of fibroblast function. Tryptase, mainly through PAR-2 activation, stimulates fibroblast migration, proliferation and production of ECM, which are key aspects of the process of fibroblasts differentiation into myofibroblats. It has already been documented that tryptase induces proliferation and synthesis of fibronectin and type I collagen by human kidney fibroblasts [111]. However, despite this initial report on the direct action of tryptase in renal cells, there have not been more studies in this particular issue. Taking into account the widespread expression of PAR-2 in the kidney, it is possible that tryptase exerts a more diversified role in renal fibrogenesis. For instance, PAR-2 activation in human PTEC triggers proinflammatory and proliferative responses [112].

Mast cell-derived fibrogenic factors

Many of the biochemical mediators contained in and released by MC have already been associated with the promotion of tissue fibrosis, mainly by the capacity to induce fibroblast transformation into myofibroblats. Among them, TGF-β1 is probably the most well-known fibrogenic mediator in kidney scarring. MC store latent TGF-β1 in their chymase-containing secretory granules which are rapidly converted by chymase into its active form upon MC degranulation [76]. This

growth factor is believed to be involved in the induction of fibroblast ECM production by MC *in vitro* [113]. bFGF is another key regulator of fibroblast function secreted by MC [114] and was shown to account for the fibrogenic role of MC in pulmonary fibrotic disorders [115]. Moreover, it was documented that cardiac MC cause atrial fibrosis though PDGF-mediated induction of fibroblast proliferation and synthesis of collagens [116]. In addition, MC-derived histamine was shown to induce the proliferation of human skin [117] and conjuntival [118] fibroblasts through its H1 and H2 receptors. Histamine is also partially responsible for MC induced effects on the functional behavior of fibroblast in an *in vitro* model of wound healing [119].

Kidney disease development in MC-deficient mice

MC-deficient mice have been used extensively as a model for studying MC specific functions in a variety of pathological scenarios. The possibility to reconstitute these mice by transplantation with BM derived-MC (BMMC) presented itself as a powerful tool to confirm that an observed outcome in MC-deficient mice is solely due to the absence of MC and not to other inherent defect of the strain. By using MC-deficient mice it was demonstrated that MC activation and degranulation have detrimental [18, 120] or beneficial [121, 122] results in acute or chronic models of kidney diseases. Disregarding the use of distinct models for the induction of kidney injury in these studies, other possible explanation for the opposite observations could be due to the employment of different strains of MC-deficient mice. Those reports that showed an adverse function of MC used the $Kit^{W\text{-}sh/W\text{-}sh}$ mice whereas the others that demonstrated the protective role of MC used the $Kit^{W/Wv}$ mice strain. $Kit^{W/Wv}$ mice have truncated and point-mutated W and Wv alleles, respectively [123], and $Kit^{W\text{-}sh/W\text{-}sh}$ mice have an inversion upstream of the Kit gene [124]. Although MC deficiency in these strains is provoked by inactivating mutations of the SCF receptor (c-kit), they exhibit quite different phenotypes. The c-*kit* mutations in $Kit^{W/W\text{-}v}$ mice cause multiple hematopoietic abnormalities, like severe macrocytic anemia and impaired T development in the thymus, as well as sterility and impaired melanogenesis. In contrast, W-sh mutations result in fewer developmental abnormalities. $Kit^{W\text{-}sh/W\text{-}sh}$ mice are fertile and have normal red blood cell numbers, and thereby are considered a better model for investigating MC biology *in vivo*. Distinct responses of these strains have already been reported in models of autoimmune diseases. While $Kit^{W\text{-}sh/W\text{-}sh}$ mouse develops full clinical and histologic arthritis induced by antibodies to type II collagen and LPS, $Kit^{W/Wv}$ mouse was resistant to this pathology, probably due the neutropenia found in this strain [125]. Moreover, $Kit^{W\text{-}sh/W\text{-}sh}$ strain is more susceptible to develop experimental autoimmune encephalomyelitis when compared with the $Kit^{W/Wv}$ mice [126]. The discrepancies showed in these studies are clearly a consequence of non-MC-related phenotype differences between these mice strains. Consequently, we should be cautious when implying the role of MC in kidney disease based on the results obtained with these two different strains.

Perspectives

Despite the attention given to the potential function of MC in the development of CKD, the mechanism by which MC numbers are increased in the setting of tubulointerstitial fibrosis is still unknown. Similar to monocytes and macrophages, MC can re-enter the cell cycle and proliferate following appropriate stimulation. Besides, increased recruitment and/or retention, and local maturation of MC progenitors can also contribute to MC accumulation in the injured kidney. SCF is paramount for MC development and is considered the major MC agonist under both physiologic and pathologic conditions, leading to MC chemotaxis, adhesion, activation, proliferation and viability. In two separate studies, SCF expression was found to be increased in the tubulointerstitium of patients with different forms of primary and secondary glomerulonephritis [127, 128]. Another possible factor involved with MC migration to the kidney is TGF-β1, which was found to be the most potent chemotactic agent described for MC, eliciting its effect at much lower molar concentrations than other known MC chemotaxins [129, 130]. Therefore, TGF-β1 released from exocytose granules upon MC activation may initiate a self-perpetuating signal that will fuel MC influx to the tubulointerstitium. Other

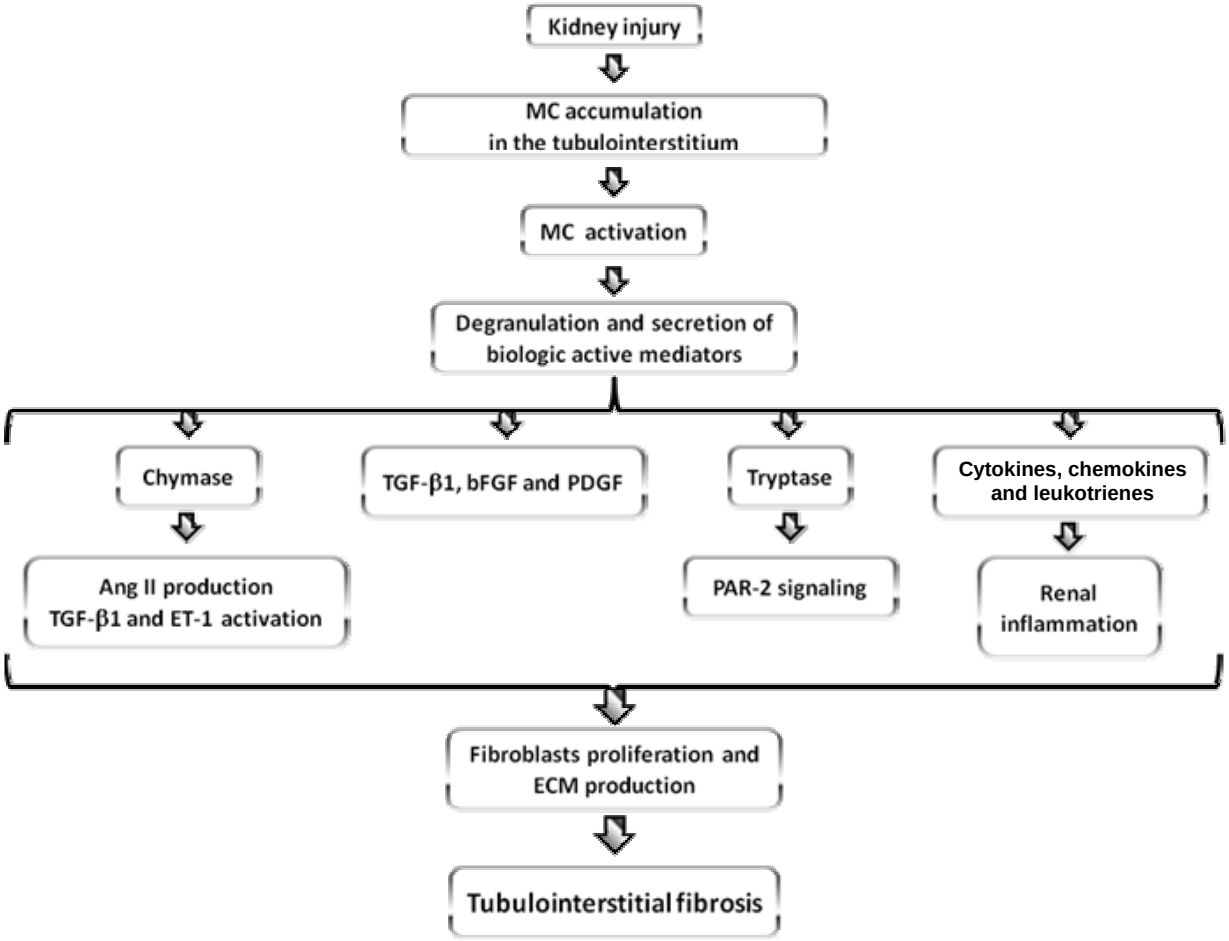

Fig. 1. Potential mechanism involved in MC participation in kidney fibrosis.

chemokines known to regulate MC migration, like RANTES [131] and MCP-1 [132], are also upregulated in the setting of kidney injury [133, 134]. If these molecules are involved in the accumulation of MC in the kidney remains to be determined.

MC proteases may be responsible for many of the activities that have been attributed to MC. The development of chymase (mMCP-4) [135] and tryptase (mMCP-6)–deficient mice strains [136] will help us to study the impact of chymase and tryptase in the overall function of MC. As mentioned earlier, mMCP-4-deficient mice have already been used in experimental models of kidney injury that obtained contrary results. Thus, chymase action on kidney disease still remains to be ascertained. The impact of MC tryptase deletion on tissue fibrosis development still has to be explored. Nevertheless, it cannot be ignored that mice contain many chymases and tryptases that are absent in humans. Thus, it is important to account for these differences when transferring findings from animal models to biological function of these proteases in humans.

Recently, Kit-independent MC-deficient mouse strains were generated by different approaches [137, 138, 139, 140]. These strains allow the separation of MC and Kit functions *in vivo*, which were impossible in the $Kit^{W/Wv}$ and $Kit^{W\text{-}sh/W\text{-}sh}$ mice. Additionally, a transgenic mouse in which a segment of the *Cpa3* promoter drives the expression of Cre recombinase was developed, allowing the employment of the Cre-lox recombination technology to delete target genes specifically in MC [141]. Studies conducted with these new strains will result in a major breakthrough

in the understanding of the physiological and pathological functions of MC.

CONCLUSION

Inflammation is an important protective response that governs wound healing and the repair processes after renal damage. However, prolonged and uncontrolled inflammation in the kidney is prejudicial, promoting tissue destruction and fibrosis, which, over time, can drive to organ failure. Therefore, therapies that aim to prevent or delay this process are highly desirable. Due to the proinflammatory and fibrogenic action of MC in a variety of pathological conditions and their association with kidney function loss in patients with CKD, these cells have become promising targets for halting kidney fibrosis. The most striking morphological feature of MC is their numerous cytoplasmic secretory granules filled with preformed compounds. MC can release a significant amount of biologically active mediators whereas other cells are just beginning to change their transcriptional programs. MC are likely to be one of the first initiators of the process of kidney inflammation and fibrosis. Further studies are warranted to extensively investigate all the aspects of the role of MC in the development of kidney scarring. The proposed mechanisms involved in the role of MC in the development of kidney fibrosis are presented in Fig. 1.

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