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Bone marrow-derived progenitor cells and renal fibrosis

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1. ABSTRACT

Bone marrow-derived cells modulate solid organ diseases. For example, the different immune cell populations mediate tissue inflammation and damage, whereas progenitor cell populations are thought to enhance tissue regeneration. However, in the process of tissue fibrosis the contribution of either cell type is less clear. Here we discuss current concepts on how different bone marrow-derived progenitor cell populations may contribute to renal fibrosis.

2. INTRODUCTION

The burden associated with the increasing prevalence of patients with chronic kidney disease (CKD) encourage the scientific community to unravel the pathomechanisms of CKD and to develop novel treatment strategies that slow down, halt or even revert CKD. In renal biopsies of patients with various types of CKD leukocytic cell infiltrates are always present in the tubulointerstitium. They have been classified as "secondary interstitial nephritis" or as "unspecific immune cell infiltrates", but whether they always represent a state of inflammation or whether they represent an unspecific response to tissue damage remains under debate. More recently additional bone marrow-derived cell populations have gained much interest, also in renal medicine, i.e. the stem cells (1). Stem cells are polypotent or oligopotent in terms of lineage differentiation and give rise to a number of different types of progenitor cells which evade from the bone marrow (BM) and migrate to sites of injury (2). Stem cells have been proposed as a new therapeutic tool to enhance damaged organ regeneration. Research in that area is compromised by the ethical concerns associated with the use of embryonic stem cells which seem to have the greatest potential for lineage differentiation. However, a number of studies suggest that other BM-derived progenitors recruit to the kidney and modulate experimental kidney disease (3).

What is the evidence that BM-derived progenitors modulate CKD? What are the signals that initiate BM-derived progenitors recruitment to the kidney? Do they specifically affect the process of renal fibrogenesis? Do different subtypes of BM-derived

Table 1. Causes of end-stage renal disease

Glomerulonephritides	25%
Diabetes mellitus type 2	15%
Interstitial nephritis (infectious)	13%
Vascular nephropathy	9%
Cystic kidney diseases	9%
Diabetes mellitus type 1	6%
Interstitial nephritis (toxic)	4%
Systemic diseases	3%
Congenital nephropathies	1%
Hereditary nephropathies	1%
Unknown causes	13%

Source: ref 11

progenitor cells have different effects on renal fibrogenesis? Can transfer of specific BM-derived progenitor cell populations be used to prevent renal fibrogenesis and may be used for the treatment of CKD? In this review we address these questions by recent data on the role of BM-derived progenitor cells in experimental models of kidney disease.

3. MECHANISMS OF RENAL FIBROGENESIS

Tissue fibrosis is often defined as a dysregulated wound-healing response (4). This repair process involves two distinct stages: a regenerative phase, where injured cells are replaced by cells of the same type, leaving no lasting evidence of damage; and a phase known as fibroplasia, or fibrosis, where connective tissue replaces normal parenchymal tissue (4). In this process fibrogenesis is required to reconstitute the extracellular matrix and to mechanically stabilize tissue defects after injury. For example, the healing phase of myocardial infarction requires replacement by tissue which can stand the mechanical stress of the beating heart. The same is true for the periost after bone fractures or the skin after penetrating injuries. In these cases fibrogenesis stops after closing the wound suggesting that the initiation and cessation of fibrogenesis is a highly regulated process, involving signals that abrogate fibrogenesis upon healing of a local defect.

The situation appears to be different in diffuse disease processes like fibrosis involving the entire lung, liver or kidney. These types of injuries do mostly develop in disease states that affect the entire organ so that anti-fibrotic signals may not appropriately balance the profibrogenic signals triggered by the underlying disease process. The underlying disease processes are mostly long-term persistent rather short-term transient, so that the production of profibrogenic signals predominates. Such profibrogenic signals include growth factors, proteolytic enzymes, angiogenic factors, and fibrogenic cytokines that stimulate the deposition of extracellular matrix molecules (4-6).

Activation of intrinsic renal cells in the glomerular or tubulointerstitial compartment leads to the release of proinflammatory cytokines which attract and activate immune cells and of profibrogenic growth factors which activate various cell types to secrete proteases as well as extracellular matrix (ECM) components (7). Thus, recruiting effector cells for danger control is always accompanied by rearrangement of the ECM. Dissecting the molecular pathways that govern these coincident and connected phenomena is still ongoing. Clearly, inflammatory cell infiltrates are the major source for profibrotic cytokines and growth factors which stimulate the secretion of ECM components and the proliferation of interstitial fibroblasts (8). Contrarily, secreted ECM components regulate the activation of immune cell infiltrates (9). Thus, the presence and the extent of immune cell infiltrates represent a strong prognostic factor for interstitial renal fibrosis and the progression of CKD to end-stage renal disease (10). Vice versa, the definition of interstitial renal fibrosis, albeit involving many different mechanisms, includes the presence of various degrees of immune cell infiltrates in CKD (Table 1) (11).

Interstitial fibroblast activation is a key step in renal fibrogenesis because interstitial fibroblasts have a large capacity to secrete ECM components even under hypoxic conditions (12). Interstitial fibroblasts are a more heterogeneous group of cells than traditionally anticipated (13). Interstitial fibroblasts in renal fibrosis originate from various sources including the resident interstitial fibroblast population, from BM-derived progenitors, and from transition of tubular epithelial cells, a process named epithelial-mesenchymal transition (EMT) (Figure 1) (4, 13-15). EMT is defined as process in which (tubular) epithelial cells loose their phenotypic characteristics and acquire typical features of mesenchymal cells. i.e. the downregulation of adhesion molecules like E-cadherin, the increased expression of matrix metalloproteinases that digest the basement membrane, and the activation of the Rac/Rho/Cdc42 family for cytoskeleton rearrangement and cell migration into the interstitial compartment (16-18). The nuclear translocation of transcription factors like beta-catenin and T cell factor/lymphocyte enchancer factor 1 (TCF/LEF1) complex, Snail1, Snail2, and Twist are also involved in this process (15, 19, 20). By contrast, the BM-derived myofibroblast progenitors are refered to as fibrocytes which represent a unique subpopulation of hematopoietic cells expressing the following surface molecules: CD34, CD11b, CD18, CD45, and HLA-DR, CCR3, CCR5, CCR7, and CXCR4 (21-25).

The contribution of each source of interstitial fibroblasts to the various types of renal fibrosis remains controvercial. Some authors point out that the contribution of EMT-derived myofibroblasts may be common in obstructive nephropathy but less common in other types of CKD (26, 27). The contribution of fibrocytes to various types of CKD has not yet been studied in great detail, possibly because the identification and quantification of this specific cell population is challenging in the diseased kidney (27). However, recent studies demonstrate that chemokine/chemokine receptor systems on fibrocytes are involved in the recruitment of circulating fibrocytes to sites of kidney fibrosis. Thus, CCL21 has been reported to act as a chemotactic stimulus for fibrocytes (28, 29). Wada *et al.* have shown

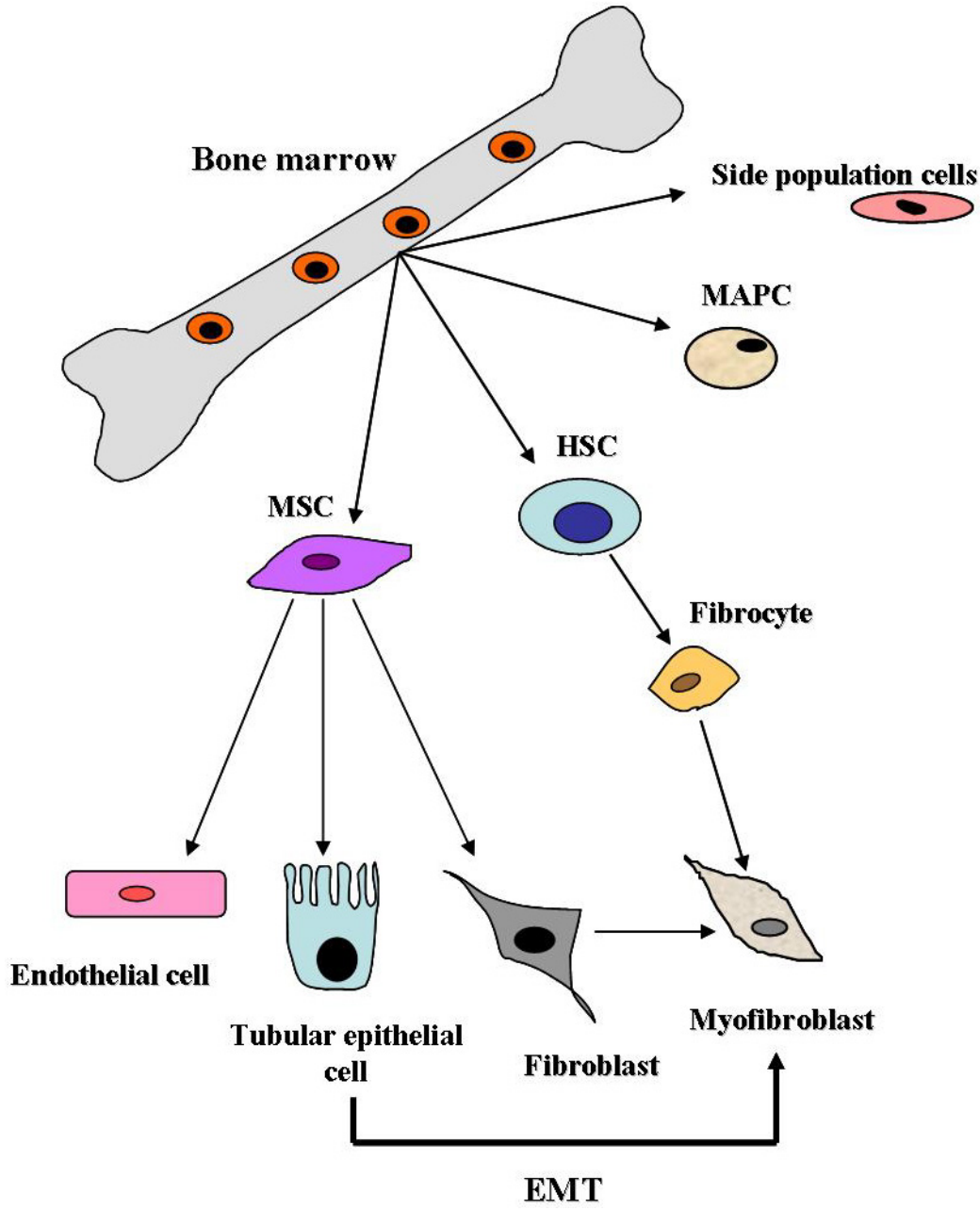

Figure 1. Involving of bone marrow-derived progenitor cells in renal fibrogenesis. Interstitial fibroblasts originate from various sources including resident fibroblasts, BM-derived progenitors and EMT (see explanation is in the text).

that blockade of CCL21/CCR7 signaling by anti-CCL21 antibodies reduced kidney fibrosis, which was confirmed by a decrease in fibrosis in CCR7-null mice with concomitant reduction in macrophage recruitment along with reduced renal transcripts of monocyte chemoattractant protein-1 (MCP-1/CCL2) (25).

Hence, it is reasonable to believe that proliferation of resident interstitial fibroblasts remains a major element in interstitial fibrosis in most types of CKD, although other pathways do exists and contribute to this phenomenon.

4. CLASSES OF BONE MARROW-DERIVED PROGENITOR CELLS

The BM harbours multiple progenitor cell populations including hematopoietic stem cells (HSC), mesenchymal stem cells (MSC), multipotent adult progenitor cells (MAPC), and side population cells (2). All of these have the capacity for self-renewal and each trait of stem cells is defined by its functional capacities rather than by the expression of distinct cell surface markers. For example, the non-adherent HSC give rise to the various

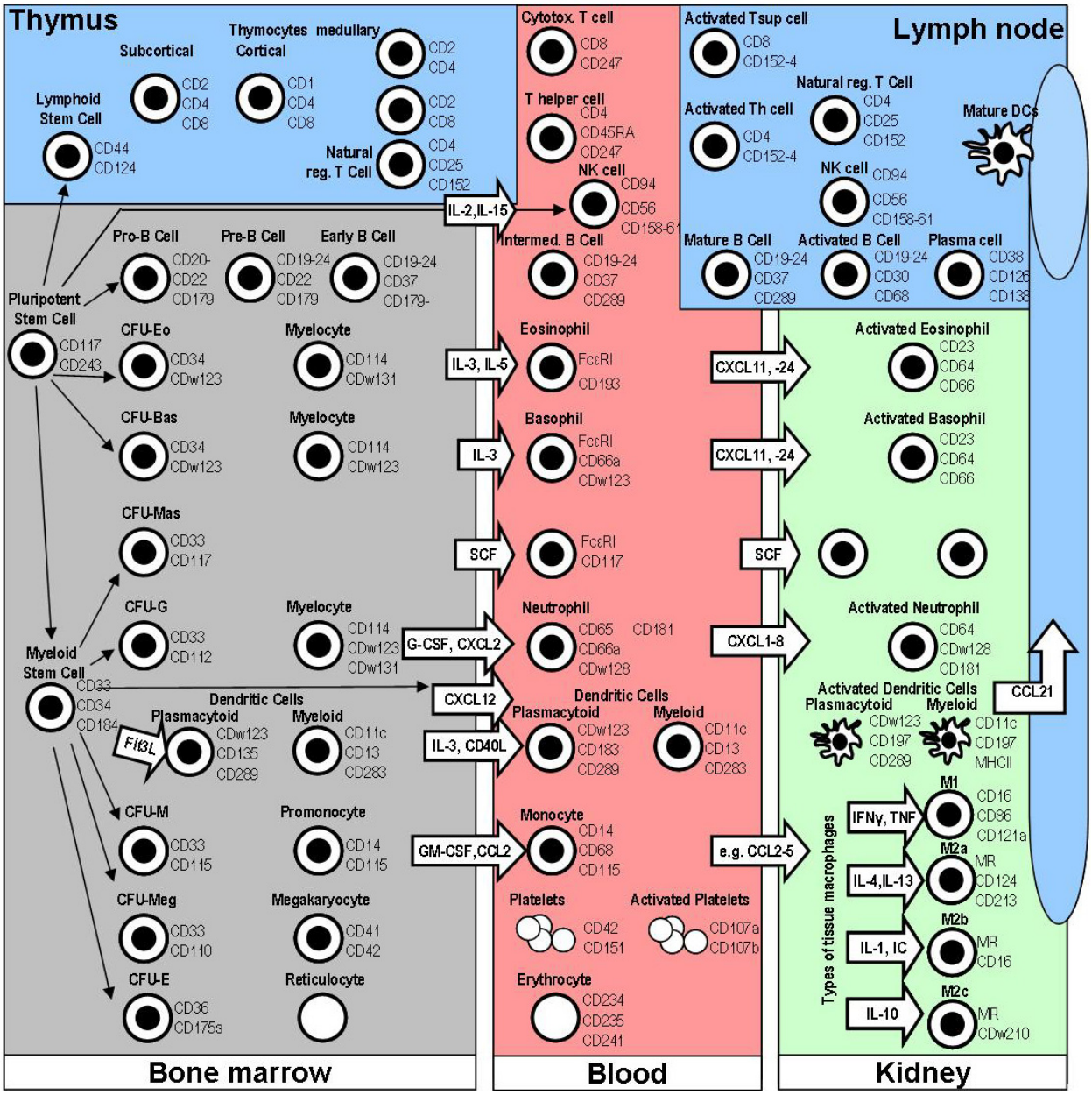

Figure 2. Cytokine-induced development and recruitment of BM-derived progenitor cell populations to the kidney.

blood and immune cell populations, i.e. leukocytes, red blood cells, and platelets (30, 31) (Figure 2).

HSC are $CD34^{+}DR^{-}$ and express surface markers like CD11b, CD27, CD45, CD34, CD41, CD14, c-kit, and Sca-1 (32, 33). The absence or low expression of other markers like Thy^{low} and Lin^{-} separates them from more differentiated immune cell populations. By contrast, MSC belong to BM stromal cells which give rise to mesenchymal cells in peripheral tissues (34). MSC have been defined by two main functions: adherent growth in culture and the ability to differentiate into osteoblasts, chondroblats, adipocytes or cardiomyocytes in response to appropriate cytokine stimuli (35-37). MSC appear as "bone lining cells" in BM biopsie and have been distinguished from HSC by the absence of CD34 and by surface expression of SH2, SH3, CD29, CD44, CD71, CD90, CD106, CD120a, and CD124. However, the expression of the markers is variable and inconsistent suggesting considerable plasticity of these progenitor cells traits. For example, CD34 is not constitutively expressed in all HSC as was previously thought. Osawa *et al.* (38) showed low expression of CD34 on HSC. Donnelly *et al.* (39) subsequently demonstrated that HSC are phenotypically heterogeneous with regard to the expreesion of CD34. Hematopoiesis can be reconstituted with $CD34^{-}$ cells (40-42). HSC, however, stroma-derived fibroblast-like $CD34^{-}$

cells can also give rise to $CD34^+$ cells with hematopoietic characteristics (33, 43).

MAPC are another highly plastic BM-derived progenitor cell population. MAPC can be grown *in vitro* from postnatal marrow and other organs of mice, rats, and humans (44, 45). Like MSC MAPC grow as adherent cells *in vitro* but unlike MSCs MAPCs can be cultured indefinitely in a relatively nutrient-poor medium. Specific growth factors induce MAPC differentiation into cells with endodermal, mesodermal, or ectodermal markers *in vitro* and *in vivo* (2).

Side-population cells are numerically a minor population of BM-derived progenitor cells. They separate from other BM-derived progenitor cells on the basis of exclusion of the fluorescent dye Hoechst 33342 using flow cytometry (46, 47). Side-population cells have a considerable potential to differentiate and integrate into other organs and they appear uncommitted to hematopoietic lineages as they lack CD34 (48-50).

5. THE ROLE OF MYELOID AND LYMPHOID CELLS IN RENAL FIBROSIS

Leukocytic cell infiltrates encompass a number of different immune cell types. Studies in animal models indicate that macrophages are the dominant infiltrating cell in the initiation and progression of injury in chronic renal disease. Resident and infiltrating macrophages play a central role in innate immune protection both through the clearance of infective pathogens and through the repair of tissue injury that occurs, in part, as a consequence of this response. For example, the initial response of macrophages to bacterial infection is cytotoxic and proinflammatory; then, on control of the infection, macrophages phagocytoze cellular debris and apoptotic bodies and begin tissue repair. However, in many noninfective renal diseases associated with macrophage infiltrates, although the primary cause may abate, interstitial inflammation and tubulointerstitial injury worsens. Direct damage to resident cells is caused through the generation by macrophages of radical oxygen species (ROS), nitric oxide (NO), complement factors, and proinflammatory cytokines. Macrophages can also affect supporting matrix and vasculature through the expression of metalloproteinases and vasoactive peptides (50). CD4 and CD8 T lymphocytes are usually present in chronic lesions. B cell infiltrates occur in diffuse and follicle-like patterns in various types of CKD (52). Neutrophils are preferentially recruited in renal infections, renal vasculitis or acute renal injury. Mast cells and basophil infiltrates are not that clearly characterized but seem to be present mostly in mixed chronic cell infiltrates (53, 54).

Eosinophils are common in acute interstitial nephritis, toxic injury or cholesterol embolism (55). What mechanisms mediate the cell type specific recruitment of these BM-derived progenitor cell types to the different compartments of the kidney? Leukocyte homing and recruitment is a highly regulated process regulated by *chemo*tactic cyto*kines*, i.e. the chemokines (56). Homeostatic chemokines mediate homing of HSC to the BM and factors like G-CSF can overcome this homing process and trigger leukocyte evasion from the BM into the intravascular compartment (Figure 2). The homing and migration process of each leukocyte subtype appears to be regulated by different chemokines or chemokine combinations which act through their respective chemokine receptors on the leukocyte surface (57). Leukocyte recruitment from the circulation into inflammatory sites is a multistep process also involving multiple other factors, like selectins, adhesion molecules, integrins and addressins (56). To leave the intravascular compartment into the kidney leukocytes need to be slowed down by transient interactions of endothelial cell selectins their corresponding partners on the leukocyte surface, i.e. rolling. The leukocyte`s arrest on activated vascular endothelial cells is mediated by chemokine-driven activation of adhesion molecules and is a prerequisite for transendothelial migration (Figure 3). After adhesion, leukocytes have to transmigrate through vascular endothelia and basement membranes to enter the interstitial compartment and continue to migrate there (58). Upon injury, intrinsic renal cells continue to produce proinflammatory cytokines that enhance the expression of adhesion molecules such as selectins and integrins and the presentation of chemokines at the luminal endothelial cell surface of capillaries adjacent to the tissue lesion (58).

The recruitment of leukocytes massively enhances the local production of cytokines and chemokines, a mechanism that sets and amplifies tissue inflammation. For example, neutrophils and macrophages generate radical oxygen species and lipid mediators that can kill pathogens but that also contribute to local tissue damage, supporting a positive feedback mechanism. This process is accompanied by the secretion of proteases which digest basement membranes and proteins (59). Macrophages themselves may secrete extracellular matrix components, but they also are the major source of growth factors such as fibroblast growth factor (FGF), transforming growth factor-beta (TGF-beta), tumor necrosis factor-alpha (TNF-alpha), epithelial growth factor (EGF), and platelet-derived growth factor (PDGF) (8, 60). The extensive remodelling of the ECM may represent an appropriate response to acute renal injury which does not necessarily result in persistent damage as matrix degradation is always accompanied by the production and secretion of novel ECM components which contribute to repair in an ongoing effort to control the cause of injury. In acute injury the secretion of proinflammatory cytokines and chemokines will finally stop and antiinflammatory mediators will calm down tissue inflammation and recruitment of leukocytes to the kidney (61). By contrast, chronic disease processes, genetic dysregulations of fibrogenesis, or coincident triggers of proinflammatory cytokines will maintain a high level of activation in renal leukocytes (62). The continuous production of profibrotic cytokines, growth factors, and chemokines provides an ongoing stimulus for renal fibrogenesis and progressive interstitial fibrosis. In that concept, renal leukocytic cell infiltrates represent amplifiers of fibrogenesis (and tubular atrophy) as they produce large amounts of signals that regulate the remodelling of renal ECM during injury. In

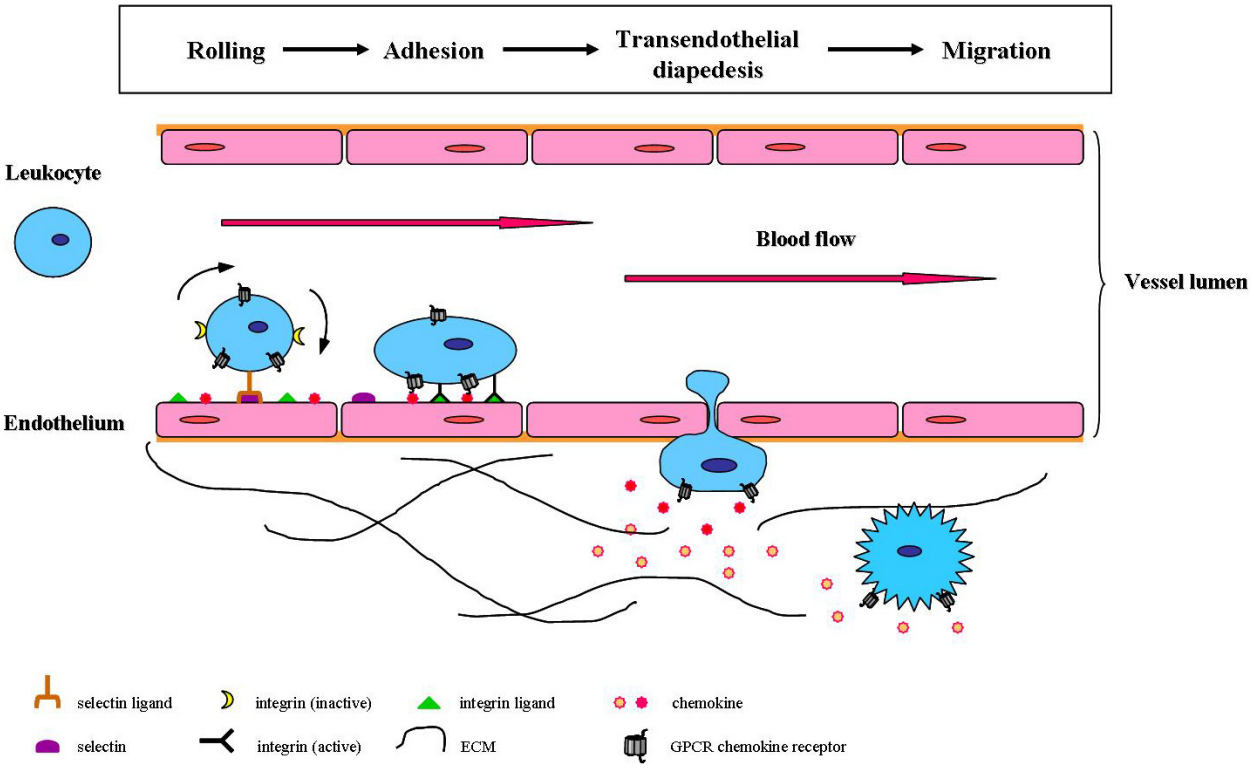

Figure 3. Multistep process of leukocyte recruitment from the circulation into inflammatory sites. Following initial selectin-mediated capture, adhesive interactions between leukocyte and activated endothelium are required for transendothelium migration of leukocytes into inflammatory site.

addition, blood-borne immature, monocyte-like cells, referred to as fibrocytes, rapidly enter sites of tissue injury and contribute to renal fibrogenesis by producing large amounts of ECM components just like fibroblasts (63). These cells need to be distinguished from MSC which are from a non-HSC origin, do not express myeloid lineage surface markers and which may transdifferentiate into fibroblasts.

The continuous stimulation of intrinsic renal parenchymal cells by infiltrating leukocytes and the recruitment of fibrocytes results in ongoing synthesis of extracellular matrix components and irreversible structural damage. In the glomerulus infiltrating macrophages stimulate mesangial cells to secrete collagen type IV, laminin, and fibronectin that contribute to the development of glomerulosclerosis (64). Mesangial expansion also leads to narrowing or obliteration of single glomerular capillaries as well as dilation of others (65). Eventually this will not only result in podocyte damage and glomerular sclerosis, but also in destruction of the entire nephron, including downstream peritubular capillaries (64, 66). Thus, the tubulointerstitial compartment undergoes major structural rearrangement. The accumulation of T cells, macrophages, and B cells provides continuous release of profibrotic mediators that induce the accumulation of fibroblasts, and the ongoing production of extracellular matrix. Activated tubular epithelial cells themselves contribute to this phenomenon by matrix production chemokine-cytokine release, and even to transdifferentiate to myofibroblasts that migrate into the interstitial space (60). The interstitial cell infiltrate itself, together with the increasing amount of extracellular matrix, lead to critical widening of the interstitial space, thereby increasing the distance of the remaining peritubular capillaries to their respective tubular segments, impairing oxygen diffusion as well as tubular reabsorption and excretory function (67). Finally, vascular rarification and diffuse scarring lead to extensive tubular atrophy, and glomerulosclerosis. The extensive loss of renal parenchyma and structural integrity finally results in end-stage renal disease with the clinical signs and symptoms of uremia. Leukocytic cell infiltrates resolve, but renal fibroblasts maintain the synthesis of extracellular matrix due to sustained hypoxia and autocrine stimulation (68, 69). Myofibroblasts contribute to contraction of the fibrous tissue with scarring, resulting in shrunken kidneys.

Contribution of immune cell subsets has been studied in different experimental models of progressive kidney diseases. For example, in collagen4A3-deficient mice (Col4A3-/-) interstitial macrophages promote the progression of Alport disease-like renal failure. Treatment with chemokine receptor 1 antagonist, known to block interstitial leukocyte recruitment, from weeks 6 to 10 of life prolonged survival of Col4A3-/- mice, associated with less interstitial macrophages, apoptotic tubular epithelial cells, tubular atrophy, interstitial fibrosis, and less globally sclerotic glomeruli (70).

In experimental model of crescentic glomerulonephritis, administration of antibodies to MCP-1 decreased the extent of proteinuria, reduced glomerulosclerosis and improved renal dysfunction (71). Reduction of macrophage infiltration and delayed neutrophil clearance in the kidney has been observed in rats with tubulointerstitial nephritis (TIN) treated with MCP-1 antibody (72). Duffield *et al.* demonstrated that macrophage depletion reduced the number of glomerular crescents, improved renal function and reduced proteinuria in murine crescentic glomerulonephritis model (73).

6. THE ROLE OF BONE MARROW-DERIVED PROGENITOR CELLS IN RENAL FIBROSIS

The concept that BM-derived progenitor cells migrate to the damaged kidney to replace functionally and structually differentiated adult renal cells remains attractive (3). However, the present data on the role of progenitor cells in renal fibrosis remain controversial. One problem remains the precise phenotypical and functional characterization of the studied progenitor cell population. Therefore, the present data does not yet provide a general interpretation for the role of progenitor cells in the diseased kidney and conclusions are limited to the specific experimental set up and technical means of cell type characterization. Do BM-derived progenitor cells contribute to matrix production in renal injury? Do BM-derived progenitor cells reconstitute intrinsic renal cells by transdifferentiation?

6.1. Do BM-derived progenitor cells contribute to matrix production in renal injury?

A smart experiental approach to this question will use a model of renal pathology caused by a genetic defect in ECM components and test whether BM-transplantation can prevent the disease by the recruitment of wild-type progenitor cells to the kidney and local secretion of the wild-type ECM component. This experimental approach was performed using Col4A3-/- mice. The homozygous deletion of the Col4A3 gene results in a renal phenotype similar to human autosomal recessive Alport syndrome (74-76). In Alport syndrome lack of the A3 chains of collagen 4 results in a modified molecular composition of the glomerular basement membrane which make it more susceptible to matrix metalloproteinase digestion (77, 78). Progressive digestion of the glomerular basement membrane is associated with activation of adjacent intrinsic renal cells, collapse of glomerular capillaries, glomeruloscleros, subsequent intersititial fibrosis and end-stage kidney disease in mice and humans (74-76). Sugimoto *et al.* (75) and Prodromidi *et al.* (76) demonstrated that transplanting wild-type BM into lethally irridiated Col4A3-/- mice can improve glomerular pathology by reconstitution of glomerular Col4A3 expression. In these studies the improved glomerular pathology was associated with less interstitial fibrosis and improved overall survival. These provide evidence for the concept that BM-derived progenitor cells recruit to damaged kidneys and that these cells can produce and integrate collagens into the ECM. While this phenomenon was supportive in the experimental setting of stem cell transplantation two important questions remain. Which cell population(s) in the BM is(are) responsible for these effects? Does this data rather support the profibrotic effect of BM-derived cells in other types of CKD? This question was also addressed using an ischemia-reperfusion model in rats. After reconstituting the rats with R26-human placental alkaline phosphatase transgenic BM transient increases in collagen III transcription and interstitial protein deposition were observed, peaking on days 7 and 28, respectively. Over time, an average of 32% of all interstitial myofibroblasts coexpressed R26-human placental alkaline phosphatase and procollagen I. Hence, a significant part of the ECM producing interstitial myofibroblasts originates from the BM (79).

6.2. Do BM-derived progenitor cells reduce fibrosis by reconstituting intrinsic renal cells?

One may speculate that BM-derived progenitor cells recruit to the injured kidney and contribute to the regeneration of endothelial cells, tubulur epithelial cells or even podocytes. Several studies in models of acute renal injury support this hypothesis. For example, in rodents, injections with HSCs have shown to contribute to tubular epithelium repair (80). In other models MSCs could restore renal tubular structure and ameliorate renal function in acute renal failure (81, 82). BM-derived progenitor cells seem to repopulate injured glomeruli of rodents at low frequency (83, 84). However, only little data the role of BM-derived progenitor cells in CKD models are available. We used the model of Col4A3-/- mice mentioned above to test the effects of weekly intravenous injection with murine MSC. The injected MSC localized to kidneys of Col4A3-/- mice but only to the interstitial compartment (74). Consistent with this finding MSC did not affect glomerular pathology in Col4A3-/- mice (Table 2). MSC localized to the lumen of peritubular capillaries and no transdifferentiation into intrinsic renal cells could be observed. It may relate to the lack of chemokine receptor CCR5 in MSC, which is required for the recruitment of leukocytes to glomeruli and transendothelial diapedesis (85). Differentiation into tubular epithelial cells or interstitial cells would require that MSC migrate from the intravascular into the tubular or interstitial compartment of the kidney. However, MSCs remained up to 7 days within peritubular capillaries. MSC treatment prevented the loss of peritubular capillaries and interstitial fibrosis, which, however, was not associated with prolonged survival of Col4A3-/- mice (74). These data support the concept that MSC recruit to the kidney and produce factors that assist to maintain the peritubular vasculature and to counterbalance renal fibrogenesis. These data also argue against the concept that interstitial fibrosis is a causal factor for renal dysfunction. Obviously, interstitial fibrosis is rather a marker of renal injury than itself detrimental for renal function.

7. SUMMARY AND PERSPECTIVE

BM-derived progenitor cells clearly migrate to renal leasions and clearly modulate to the process of renal fibrogenesis. The various lineages of BM-derived

Table 2. Studies with bone marrow–derived progenitors in collagen4A3-deficient mice with progressive renal fibrosis

Study	**Ninichuk** *et al.* (74)	**Sugimoto** *et al.* (75)	**Prodromidi** *et al.* (76)	
Mice strain	SvJ/129 Col4A3-/-	C57BL/6 Col4A3-/-	C57BL/6 Col4A3-/-	
Irradiation (Gy)	No	10 Gy	8 Gy	
BM and/or MSC transplantation	MSC	BM	MSC	BM
Cell count/mouse	$1x10^6$	$2\text{-}5x10^6$	$1x10^7$	$5x10^5$
Administration/Injection	i.v.	i.v.	i.v.	i.v.
Proteinuria	No improvement	Improvement	No improvement	Improvement
BUN Serum creatinine	No improvement	Improvement	No improvement	Improvement
Renal hisology (glomerular injury and interstitial fibrosis)	Did not affect in glomerular injury ↓interstitial fibrosis	↓ glomerular damage ↓ interstitial fibrosis	No improvement	↓ glomerular damage ↓ interstitial fibrosis

progenitor cells have different functions in this process and act on renal fibrogenesis through different mechanisms. There is good experimental evidence to support a profibrogenic effect of most leukocyte subsets which secrete proinflammatory cytokines and profibrotic factors during acute and chronic renal injury. Obviously, fibrocytes represent a BM-derived cell population of HSC origin. Fibrocytes specifically recruit to the renal interstitium and contribute to the heterogeneous pool of interstitial fibroblasts. The role of other BM-derived progenitor cell populations is less clear. For example, the current classification of MSC may still encompass cell types with different functional properties. Some studies suggest their transdifferentiation into renal cells, some studies suggest that they counterbalance renal fibrogenesis by maintaining the peritubular vasculature. Recent data also question the causal role of fibrogenesis for renal dysfunction. Interstitial fibrogenesis appears rather to be a marker of tissue remodelling while tubular atrophy and secretory renal dysfunction is more a consequence of immune cell-mediated apoptosis of tubular cells and endothelial cells of peritubular capillaries. The field remains open for novel discoveries and, possibly, for novel therapeutic targets that can help to modulate renal fibrogenesis and the progression of CKD.

8. ACKNOWLEDGEMENT

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Abbreviations: CKD: chronic kidney disease, BM: bone marrow, ECM: extracellular matrix, EMT: epithelial-mesenchymal transition, HSCs: hematopoietic stem cells, MSCs: mesenchymal stem cells, MAPC: multipotent adult progenitor cells, TCF/LEF: T cell factor/lymphocyte enhancer factor 1, FGF: fibroblast growth factor, TGF-beta: transforming growth factor-beta, TNF-alpha: tumor necrosis factor-alpha, EGF: epithelial growth factor, PDGF: platelet-derived growth factor, Col4A3-/-: collagen4A3-deficient mice, TIN: tubulointerstitial nephritis, CCR1: chemokine receptor 1, MCP-1: monocyte chemoattractant protein-1, BUN- blood urea nitrogen

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