M2 macrophage in Fibrosis and kidney graft rejection

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Abstract

Commonly macrophages are categorized into M1 and M2 subsets. M1 macrophages are defined as inflammatory cells and may contribute to tissue injury, while, M2 macrophages play a central role in tissue remodeling and control of immune responses. It seems that the existence of these cells in graft location is effective for control of inflammation and improvement of transplantation consequences. Although, the relative contribution of M2 cells in organ transplantation is not clear, the accumulation of these cells in acute and chronic injury models of transplantation was shown. In some cases, the depletion of M2 cells lead to amelioration of disease; however in other causes, skewing the response in M2 cells lead to augmentation of graft fibrosis and worsening of graft condition. In spite of these findings, the benefits of such strategies and their implications in human disease are not clearly understood. The purpose of this mini-review is to highlight the role of alternatively activated M2-type macrophages in the improvement or reduction of the kidney transplantation outcome.

Keywords: M2 macrophages, Fibrosis, kidney, Graft rejection

Introduction

Macrophages are derived from circulating peripheral mononuclear cells which enter into tissues and become residential during normal leucocyte re-circulation or during inflammatory responses (1). In human being, the main monocyte populations are composed of classical, intermediate and non-classical subsets. Classical monocytes account for 90-95% of circulating monocytes that migrate to different tissues and are well known as $CD14^{hi}$ CD16− CD64+ $CCR2^{hi}$ $CX3CR1^{low}$ CD62L+ monocytes. These cells are characterised by their phagocytic and microbicidal activity and low pro-inflammatory cytokine production. Intermediate monocytes are minor sub-population with CD16+ CD14hi $CCR2^{low}$ $CX3CR1^{hi}$ CD16+ CD64+ characteristics and show pro-inflammatory-activity and produce tumour necrosis factor alpha (TNF-α) (in response to LPS) as well as interleukin-1 beta (IL-1β) and IL-6. The $CD14^{low}$ $CD16^{hi}$ $CCR2^{low}$ $CX3CR1^{hi}$ CD64 cell subsets which are known as non-classical monocytes comprise 5-10% of the total macrophages and show anti-inflammatory activity and constitutively produce IL-1RA (2-4). All types of macrophages, as differentiated monocytes, play role in immune surveillance and could sense a wide spectrum of microbial antigenic patterns, immune complexes, apoptotic or necrotic cells and various mediators secreted from other cells (5-8). They become activated in response to several PAMPs, which allow them to phagocytose and eliminate pathogens, maintaining tissue integrity in an immunomodulatory manner (9, 10). Recently, an experimental model has been developed to define the complex mechanism of polarization and activation of macrophages towards the classical (M1) or the alternative (M2) state (9, 11). Bacterial cell wall components, lipoproteins, intracellular pathogens and cytokines such as TNF-α and interferon gamma (IFN-γ) may induce the M1 activation pathway. The main features of M1 macrophages are the secretion of inflammatory cytokines and production of nitric oxide (NO) following receptor-ligand interaction (12-14). In contrast, activation of M2 cells is induced by cytokines such as tumour growth factor beta (TGF-β), macrophage colony stimulating factor (MCSF), IL-4, IL-13, IL-10, as well as immune complexes and
complement activation by products and organisms such as parasites, fungi and apoptotic cells (12). The anti-inflammatory M2 macrophages stimulate angiogenesis, promote cell proliferation and reduce apoptosis by secreting regeneration stimulating factors (15). Regarding to the role of M2-derived products in promotion of tissue repair; it seems that the *ex vivo* modulation of macrophages to M2 phenotype may be applied for suppression of immune response and promotion of tissue remodelling in kidney transplantation (16).

Alternatively activated macrophages

The concept of alternative activated macrophages was defined in the early 1990s and the nomination of ‘alternatives’ were derived from induction of this cells by IL-4 rather than by IFN-γ (17, 18). The M2 macrophages turn off the damaging mechanisms of immune system activities by production of anti-inflammatory cytokines. M2 is the phenotype of resident tissue macrophages and can be further activated by IL-4. In addition to their excellent phagocytic capacity, M2 macrophages produce high levels of IL-10, TGF-β and low levels of IL-12 (19). Moreover, M2 macrophages produce angiogenic and extracellular matrix (ECM) components which are involved in tissue turnover (20). The M2 macrophages also clear

damage-associated molecular patterns (DAMPs) and apoptotic cells which regulate inflammatory responses and promote wound healing and tissue repair (21). Despite the anti-inflammatory and regulatory effects of M2 macrophages, they can induce allergic inflammation and promote growth of tumours (22, 23). The current classification of M2 macrophages is based on type of stimuli and the gene transcription or protein expression of M2 markers. M2 macrophages could be subdivided into M2a, M2b, M2c and M2d types based on their stimulatory source of activation (24, 25) (26, 27). IL-4 and IL-13 are the main stimuli for the induction of M2a activation (Figure 1), while bacterial lipopolysaccharides (LPS) and immune complexes may stimulate M2b cells. Moreover, glucocorticoids and TGF-β stimulate M2c cells and IL-6 and adenosines are needed for activation of M2d cells (28). Recently, classification of the M2 macrophages was performed based on the activation of stimulatory factors. In this subdivision, the M2a group is called M(IL-4) and M2b is called M(IC), and the M2c includes M(IL-10), M(GC+TGF-β) and M(GC). Given that a wide range of other signals is needed to induce M2 macrophage activation, this classification still fails to cover M2 subdivision. In addition, the *in vivo* translation of these M2 subdivisions is difficult (12). Moreover, tissues may contain mixed macrophage populations with a spectrum of activation states (29).

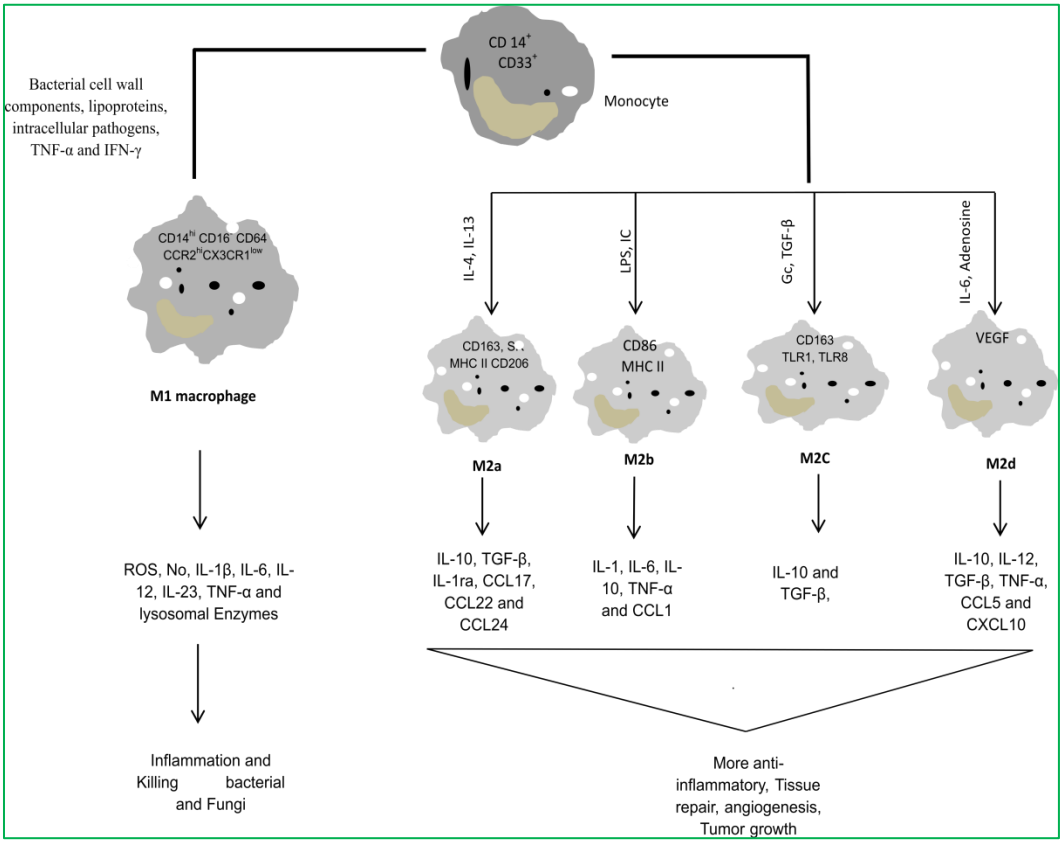

FIGURE1. Macrophage polarization. Classically activated (M1) and alternatively activated (M2) phenotypes. TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-beta; MR (CD206), mannose receptor; NO, nitric oxide; ROS, reactive oxygen species; SR, scavenger receptor; VEGF, vascular endothelial growth factor; GCs, glucocorticoids; ICs, immune complexes; IL1-ra, IL-1 receptor antagonist; TLR, Toll Like Receptor.

Clinical signs, such as interstitial fibrosis, tubular atrophy and glomerulosclerosis occur during chronic renal allograft failure (30). Among these, fibrosis is the hallmark pathological feature that develops before occurrence of any significant clinical dysfunction (31). Inflammatory processes such as cell-mediated/ antibody-mediated rejection, or non-immune events such as hypertension and ischaemia reperfusion injuries are common causes of fibrosis in transplanted tissues (32, 33). Recent studies in the rodent models of ischaemia reperfusion of renal injury have shown that a strong influx of neutrophils, macrophages and lymphocytes occur in response to pro-inflammatory cytokines, moreover, expression of chemokines such as IL-6, IL-8 and monocyte chemoattractant protein 1 (MCP-1) is elevated (34-36). Production of reactive oxygen species (ROS) and creating a pro-apoptotic environment by recruited cells can mediate injury in ischaemia reperfusion model (37); While, blocking of pro-inflammatory cytokines or depleting of neutrophils and lymphocytes may hinder acute injury (38). Some studies show that CCL2 and CCL3 are crucial chemokines for recruitment of macrophages (39, 40). Th2 cytokines (IL-4, IL-13) promote M2 macrophages phenotype and, subsequently, inflammatory fibrosis can be induced by TGF-β secreted from M2 macrophages (41, 42).

Recently, Lee et al. showed that in the course of ischaemic renal injury the infiltration of macrophages has a particular pattern. So that within the first 24h the M1 phenotype is predominant, while five to seven days after reperfusion the M2 phenotype surmount the others (43). Some studies suggest that following reperfusion, macrophages may play role in the immediate injury response but these cells may then transit to a 'trophic phenotype' to support tubular epithelium repair. There is another animal model of inflammatory renal injury with kidney fibrosis and interstitial inflammation (43, 44). In the unilateral urinary outlet obstruction (UUOO) model that completes clamping of one ureter, this results in reduced renal blood flow and reduced glomerular filtration rate within 24h. In this model, M2 macrophages may be present and contribute through modulation of apoptosis and cell survival signals (43). Recently, studies have shown blockade of microRNA 21 (miR21) leads to reduction in macrophage infiltration and production of pro-fibrotic factors, such as TGF-β1, with an attenuation in renal fibrosis (44).

In some studies, significant correlation between interstitial fibrosis and accumulation of CD68 + CD163+ M2-type macrophages have been identified by immunostaining. Therefore, amelioration of acute and chronic injury in experimental models following the depletion of macrophages has indicated the role of these cells in the injury models (45, 46). However, the implications of such strategies in human disease are not known.

In renal fibrogenesis, a T-helper2 (TH2)-prone inflammatory milieu promotes M2 macrophages recruitment and activation in a MyD88-dependent manner (Figure 2). However, TLR2, TLR4 and MyD88 knockout (KO) mice demonstrates reduced TH2 cytokine production, lower M2 macrophage infiltration (IL-10+ and CD206+ CD11b high cells), and decreased fibrosis formation with an improved renal function. Moreover, in this model, absence of IL-4 was associated with better renal function, and in IL-13 and TGF-β levels led to a decrease in arginase activity and fibrosis formation, compared with IL-12 KO and wild-type (W-T) animals (47).

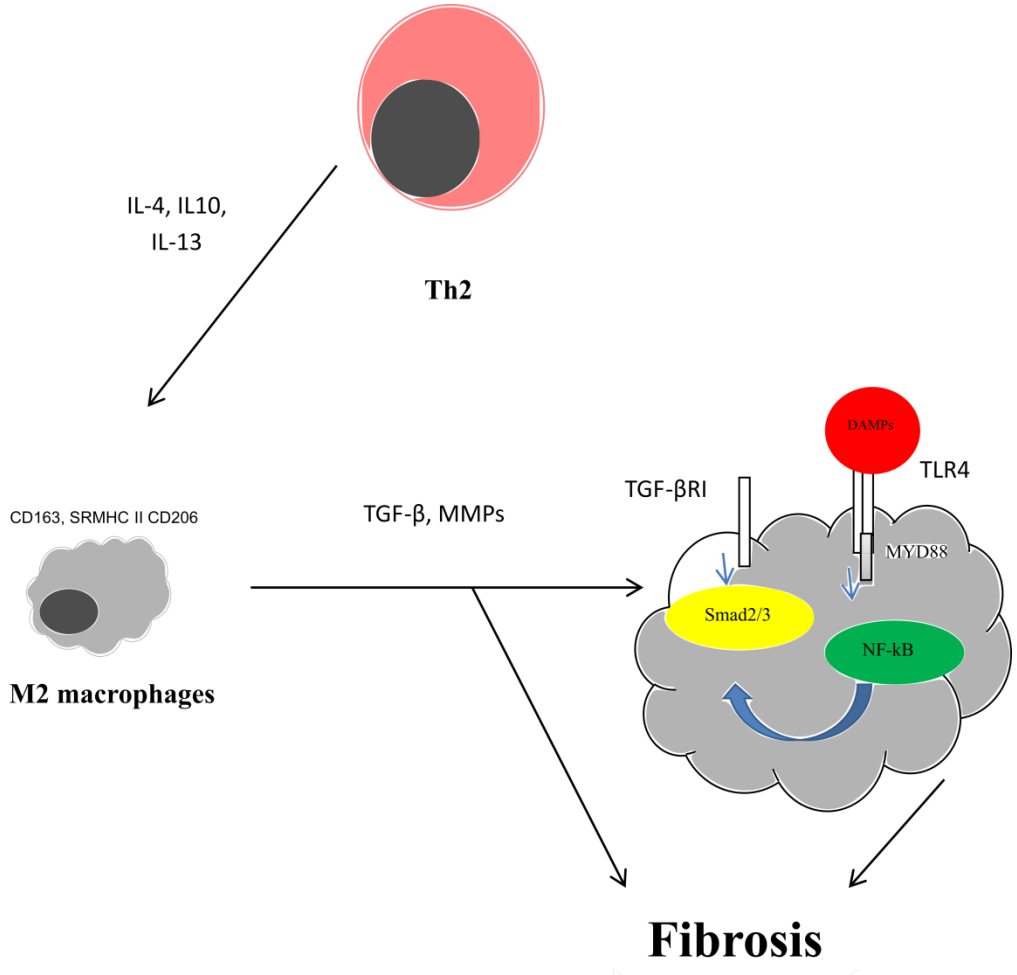

FIGURE2. Fibrosis formation mediated by MYD88 Signaling. In renal fibrogenesis, a T helper2 (TH2)-prone inflammatory milieu promote M2 macrophages recruitment and activation in a MyD88- dependent manner. TLR4 signaling enhances TGF-β signaling in renal tubular cells. TGF-β accompanying MMPs trigger fibrogenesis.

In mice, protection of acute kidney injury from renal function impairment and severe tubular injury was demonstrated during *in vivo* infusion of mesenchymal stem cells (MSCs), accompanied by a time-dependent increase in CD206-positive M2 macrophage infiltration. In addition, *in vitro* co-culture of macrophages with MSCs resulted in an anti-inflammatory M2 phenotype, with an increased expression of CD206 and secretion of IL-10 (48).
Moreover, human mesenchymal stem cells promote regeneration ischaemia-reperfusion injury via alteration of the phenotypes of macrophages and supporting the transition from tubule injury to tubule repair (48, 49).

Migration of human umbilical cord-derived stromal cells (HUCSCs) into injured kidneys improves renal function by reduction of the infiltration of macrophages in the mouse model of renal IRI. Also, increase in M2-like macrophages was shown during repair, which is beneficial

for an accelerated recovery. Thus, HUCSCs are effective in ameliorating mouse renal IRI possibly by skewing of the infiltrated macrophages into the M2 phenotype (50).

Injection of amniotic fluid stem cells in treated mice resulted in delayed progression of renal fibrosis and an increase in levels of IL1-RII, typical of an M2 macrophage phenotype. The presence of M2 macrophages led to promotion of tissue remodelling versus progression of fibrosis (51).

Renal fibrosis usually predisposes end-stage renal disease (ESRD). Studies have reported an important correlation between TGF-β1and bone morphogenic protein 7 (BMP7) in the epithelial-to-mesenchymal transition (EMT) of renal tubular epithelial cells during chronic renal injury. Unlike BMP7, TGF-β1 induces renal fibrosis by promotion of the epithelial-to-mesenchymal transition. After renal injury in a mouse unilateral ureteral obstruction (UUO) model, the recruited macrophages are polarised to a M2 subtype. Released high levels of TGF-β1 by M2 macrophages suppress BMP7 and enhance EMT-induced renal fibrosis. Depletion of M2 macrophages, but not of M1 macrophages, inhibits EMT and subsequently the renal fibrosis. Also, adoptive transplantation of M2 macrophages deteriorated renal fibrosis in the UUO renal fibrosis model (52)]. As mentioned above, IL-4/IL-13-induced M2a macrophages are tissue repairers. This function depends on upregulation of TGF-β and arginase, as well as their ability to produce certain ECM components (53-55). TGF-β produced by IL-4-activated M2a cells is a powerful activator of fibroblast collagen production and partly responsible for collagen production and enhancement of fibroblast proliferation (54, 56, 57)]. Rodent M2a macrophages also produce arginase, which has been suggested to be important for tissue repair (53, 58). Produced polyamines, such as proline via arginase-arginine pathway, resulted in cell proliferation and collagen synthetase (59). M2 Macrophages promoting fibroblast collagen synthesis via arginase and TGF-β, these cells are capable of synthesising Extracellular Matrix (ECM) components, including fibronectin, collagen type VI and βIG-H3 (60, 61)]. The βig-h3 is a TGF-β-induced ECM protein that induces the secretion of MMPs (matrix metalloproteinases) (62).

BIG-H3 promotes the adhesion and migration of monocytes, fibroblasts and keratinocytes and increases fibroblast collagen production (63-65). Perhaps the strongest evidence for the early-M1/late-M2 paradigm and for switching from a pro- to an anti-inflammatory phenotype is the pattern of pro-inflammatory cytokine production by tissue-repair macrophages. For instance, in cases of skeletal muscle and skin injury, M1 activator IFN-γ is upregulated rapidly and is required for proper healing of these tissues (66, 67). In models of renal disease, including allograft injury, glomerulonephritis and interstitial fibrosis modulating macrophage phenotype and function, have been reported to reduce renal injury (68-72). In mice with chronic inflammatory renal disease, injection of ex vivo manipulated splenic macrophages (stimulated with IL-4/IL-) can reduce renal injury and facilitate repair by downregulating inflammatory cytokine and chemokine expression of the host infiltrating macrophages (15, 72). In models of glomerular disease, the protective effect of the transplanted macrophages was associated with M2 skewing of host macrophages (73, 74). The transfer of macrophages transduced with an NF-κB inhibitor into a rat model of nephrotoxic nephritis, resulted in a reduction in iNOS and MHC class II expression in glomeruli. However, injection of ant-inflammatory macrophages consisted of only 15% of the glomerular macrophages; they could significantly reduce activation of host macrophages and glomerular infiltration that resulted in the attenuation of renal injury (73).

Transplantation of renal allografts is an established treatment for patients with chronic renal failure (75). Studies on acute kidney injury models show that macrophages are key mediators of

the onset inflammatory injury; however, more recent studies indicate a reparative role depending on macrophage phenotype. Study of the mouse kidney allografts and kidney acute tubular necrosis demonstrated that expression of activation markers of alternative macrophage in allografts is associated with molecules that induce development of M2 macrophage phenotype including IL4, IL13 and inhibin A. In this regard, increased expression of alternative macrophage activation markers and inhibin was shown in kidneys of the patients with acute tubular necrosis injured by ischaemia/reperfusion (76). Despite IFN-γ activated macrophages, kidneys undergoing T-cell-mediated rejection progressively occur in the presence of alternative activation phenotype-dependent IL4 and IL13. Similar to acute tubular necrosis, high alternative macrophage activation transcription levels in rejecting allografts are strongly associated with parenchymal deterioration (36, 76). Defects in IFN-γ, or MHC class I products, develop accelerated necrosis in mouse kidney allografts (77). IFN-γ-induced donor class I products deliver inhibitory signals to host inflammatory cells via perforin and granzymes (78). Microarrays analysis cleared that, compared to wild-type (W-T) allografts, class I-deficient allografts (class I-suppressed transcripts [CISTs]) and IFN-γ-deficient allografts (IFN-γ-suppressed transcripts [GSTs]), were associated with alternative macrophage activation markers such as macrophage mannose receptor 1 (Mrc1), arginase I (Arg1) and macrophage elastase (Mmp12) (78).

CCR5

The chemokine (C-C motif) receptor 5 (CCR5) deficiency mice (Ccr5−/− C57BL/6), as kidney recipients, show a significant reduction in glomerular damage, vascular rejection, tubulointerstitial inflammation and numbers of CD4+, CD8+, CD11c+ and alpha smooth muscle actin (α-SMA)+ cells seven and 42 days after transplantation. In the recipient mice, unlike mRNA expression of Th2-associated markers, Th1-associated markers decreased during the time (79). In addition to these findings, markers of M2 macrophages (arginase 1, chitinase 3-like 3, resistin-like alpha, mannose receptor), were strongly upregulated (mRNA and/or protein level) only in allografts Ccr5−/− recipients. Ccr5 deficiency shifted intragraft immune responses during the chronic phase towards the Th2 type and led to accumulation of M2 macrophages. Hence, CCR5 deficiency promotes monocyte polarisation to alternative macrophage activation (79).

Liver X receptors (LXR)-α, β

Liver X receptors (LXR)-α,*β* regulate intracellular cholesterol homeostasis and inhibit inflammatory gene expression (80). In the F344-LEW rat kidney transplant model, (LXR)-α, β-agonist GW3965 significantly improved function and morphology of rat kidney allografts by substantial reduction of mononuclear cell infiltrate and fibrosis. *In vitro*, LXR activation by GW3965 increases the induction of alternative activation of bone marrow-derived macrophages (BMDMs) by IL-4/IL-13. This finding suggests an additional mechanism by LXRs to prevent graft damage. This results reveals the role of macrophage LXRα in allograft rejection and prevention of fibrosis in acute and chronic organ transplantation(81, 82).

TGF-β

Biopsies of cases with non-rejected kidneys (NRK), acute rejection (AR) and chronic allograft nephropathy (CAN), for the expression of TGFβ-1 and TNF-α and the proportion of macrophages and eosinophils in the development of interstitial fibrosis (28) and graft atherosclerosis, showed the proportion of M2 macrophages that produced TGF-β was 10%–40% of the infiltrated cells in the specimen (83). Recent studies suggested M2 macrophages are involved in the progression of chronic kidney allograft injury (CAI). The results of biopsies identified a significant increase in interstitial fibrosis with accumulation of CD68+ CD163+ M2-type macrophages in children undergoing transplantation diagnosed with CAI. Localisation of M2 macrophages frequently induces interstitial fibrosis by type I collagen deposition and accumulation of α-smooth muscle actin (α-SMA) + myofibroblasts (84).

transglutaminas

In the rat renal allografts (Fischer-344 to Lewis) model of chronic allograft injury (CAI), leukocytes accumulated in blood vessels express transglutaminase (Tgm2), a multifunctional protein that is an established marker of M2 macrophages that are involved in acute and chronic graft rejection. After the resolution of acute rejection, leukocytic Tgm2 levels are lower (85).
Ischaemia-reperfusion (IR) injury is one of the causes of acute and chronic graft rejection (86).

Kidney injury molecule-1

Using mesenchymal stem cells (MSCs) after IR reduces proximal tubule kidney injury molecule-1(KIM-1) expression by inducing an anti-inflammatory ‘M2’ phenotype gene expression. MSCs are home to injured kidneys and promote repair, which may be mediated by their ability to promote M2 macrophage polarisation (87).

Conclusion

Macrophages are a critical component of an immune system that contributes to repair and regeneration in numerous tissues, but may also contribute to chronic tissue damage and fibrosis. A broad spectrum of functional macrophages phenotypes can be produced by different stimuli and this distinct population likely contributes to the contradictory roles of macrophages in tissue injury, fibrosis and regeneration. An undeniable role of macrophages in the worst late transplant outcome and allograft rejection has been proven in many studies. In more detail, their pathophysiology in injury models of the kidney has provided implications for the management of solid organ allografts. Current clinical assessment of cellular rejection suggests M1 and M2 macrophages have a distinct role in transplantation. M1 cells mainly contribute to tissue injury and graft rejection by producing pro-inflammatory cytokines and chemokines. However, M2 macrophages produce anti-inflammatory cytokines and play a central role in the modulation of immune responses, angiogenesis, tissue remodelling and repair. In many studies, accumulation of M2 macrophages has been shown in acute and chronic injury models. In some cases, amelioration of disease has reported that depletion of M2 cells and in other cases, the presence of M2 cells, has led to an increase in graft fibrosis and inferiority of graft condition. Furthermore, human clinical studies have shown M2 cells improve graft outcome by amelioration of renal

allograft inflammation. However, other studies have reported M2 macrophages produce mediators, such as TGF-β (tumour growth factor-β), VEGF (vascular endothelial growth factor) and MMPs (matrix metalloproteinases) that increase renal fibrosis and graft rejection. In addition, TH2 cytokines (IL-4, IL-10 and IL-13) skew monocyte to M2 cells, thereby these cells are predictive of fibrosis and graft rejection in a mechanism in which innate immune response is triggered in a MyD88-dependent pathway. Clearly, additional studies are needed to identify the exact mechanism of injury and determine if this may be an important therapeutic pathway in humans. Therefore, according to current studies, tissue injury or repair by M2 macrophages exhibits complex and heterogeneous phenotypes. There is no conclusive evidence about the role of these cells in graft outcome and many open questions remain in this regard. Whereas M2 cells are known to promote cell proliferation, angiogenesis, wound debridement, matrix remodelling and tissue-repair, it remains to be seen about the mechanisms by which these M2 macrophages accomplish these functions. The actual factors that regulate M2 cells phenotype during tissue repair are unknown, whereas many potential modulators of M2 macrophages activation have been identified *in vitro*. It is not clear whether different phenotypes of macrophages during the kidney inflammatory are derived from distinct migrated blood-monocyte populations or from existing wound M2 macrophages that change in phenotype. Furthermore, rodent and human M2 macrophages maybe exhibit dissimilar responses to *in vitro* activation, and it remains to be determined whether tissue injury and repair are a species-dependent difference in M2 macrophages function during *in vivo*. Finally, regulation of the tissue-repair environment and M2 macrophages phenotype will provide insight into novel therapies based on manipulating the function of M2 cells to promote tissue repair and improve graft outcome. This review identified double-edged effects of M2 macrophages in the formation of renal fibrosis and renal allograft function. Further studies are needed for more precise identification of the role of M2 macrophages in renal allograft outcome. Thereby, for better renal outcomes and decreased fibrosis formation, therapeutic strategies should be accompanied by the modulation of the TH2 and M2 cells.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the Iranian Journal of Basic Medical Sciences.

References

1. Mannon RB. Macrophages: Contributors to Allograft Dysfunction, Repair or Innocent Bystanders? Current opinion in organ transplantation. 2012;17(1):20.
2. Wong KL, Tai JJ-Y, Wong W-C, Han H, Sem X, Yeap W-H, et al. Gene expression profiling reveals the defining features of the classical, intermediate, and nonclassical human monocyte subsets. Blood. 2011;118(5):e16-e31.
3. Zimmermann HW, Seidler S, Nattermann J, Gassler N, Hellerbrand C, Zernecke A, et al. Functional contribution of elevated circulating and hepatic non-classical CD14CD16 monocytes to inflammation and human liver fibrosis. PloS one. 2010;5(6):e11049.
4. Hijdra D, Vorselaars AD, Grutters JC, Claessen AM, Rijkers GT. Differential expression of TNFR1 (CD120a) and TNFR2 (CD120b) on subpopulations of human monocytes. J Inflamm (Lond). 2012;9(1):38.
5. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. Nature reviews immunology. 2011;11(11):723-37.
6. Takeda K, Akira S. Toll-like receptors in innate immunity. International immunology. 2005;17(1):1-14.
7. Winau F, Hegasy G, Kaufmann SH, Schaible UE. No life without death—apoptosis as prerequisite for T cell activation. Apoptosis. 2005;10(4):707-15.
8. Akira S, Misawa T, Satoh T, Saitoh T. Macrophages control innate inflammation. Diabetes, Obesity and Metabolism. 2013;15(s3):10-8.
9. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. The Journal of clinical investigation. 2012;122(122 (3)):787-95.
10. Novak ML, Koh TJ. Macrophage phenotypes during tissue repair. Journal of leukocyte biology. 2013;93(6):875-81.
11. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000prime reports. 2014;6.
12. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity. 2014;41(1):14-20.
13. Benoit M, Desnues B, Mege J-L. Macrophage polarization in bacterial infections. The Journal of Immunology. 2008;181(6):3733-9.
14. Mege J-L, Mehraj V, Capo C. Macrophage polarization and bacterial infections. Current opinion in infectious diseases. 2011;24(3):230-4.
15. Ricardo SD, Van Goor H, Eddy AA. Macrophage diversity in renal injury and repair. The Journal of clinical investigation. 2008;118(11):3522-30.
16. Wang Y, Harris DC. Macrophages in renal disease. Journal of the American Society of Nephrology. 2011;22(1):21-7.
17. Reyes J, Terrazas L. The divergent roles of alternatively activated macrophages in helminthic infections. Parasite immunology. 2007;29(12):609-19.
18. Gordon S. Alternative activation of macrophages. Nature reviews immunology. 2003;3(1):23-35.
19. Galdiero MR, Garlanda C, Jaillon S, Marone G, Mantovani A. Tumor associated macrophages and neutrophils in tumor progression. Journal of cellular physiology. 2013;228(7):1404-12.
20. Badylak SF. The extracellular matrix as a biologic scaffold material. Biomaterials. 2007;28(25):3587-93.
21. Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M. Macrophage plasticity and polarization in tissue repair and remodelling. The Journal of pathology. 2013;229(2):176-85.
22. Moreira AP, Hogaboam CM. Macrophages in allergic asthma: fine-tuning their pro-and anti-inflammatory actions for disease resolution. Journal of Interferon & Cytokine Research. 2011;31(6):485-91.

23. Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends in immunology. 2002;23(11):549-55.
24. Bai J, Adriani G, Dang T-M, Tu T-Y, Penny H-XL, Wong S-C, et al. Contact-dependent carcinoma aggregate dispersion by M2a macrophages via ICAM-1 and β2 integrin interactions. 2015.
25. Colin S, Chinetti-Gbaguidi G, Staels B. Macrophage phenotypes in atherosclerosis. Immunological reviews. 2014;262(1):153-66.
26. Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers. 2014;6(3):1670-90.
27. Weagel E, Smith C, Liu P, Robison R, O'Neill K. Macrophage Polarization and Its Role in Cancer. J Clin Cell Immunol. 2015;6(338):2.
28. Duluc D, Delneste Y, Tan F, Moles MP, Grimaud L, Lenoir J, et al. Tumor-associated leukemia inhibitory factor and IL-6 skew monocyte differentiation into tumor-associated macrophage-like cells. Blood. 2007;110(13):4319-30.
29. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nature Reviews Immunology. 2005;5(12):953-64.
30. Joosten SA, Sijpkens YW, Van Kooten C, Paul LC. Chronic renal allograft rejection: pathophysiologic considerations. Kidney international. 2005;68(1):1-13.
31. Toki D, Zhang W, Hor K, Liuwantara D, Alexander S, Yi Z, et al. The role of macrophages in the development of human renal allograft fibrosis in the first year after transplantation. American Journal of Transplantation. 2014;14(9):2126-36.
32. Fadili W, Allah MH, Laouad I. Chronic renal allograft dysfunction: risk factors, immunology and prevention. Arab journal of nephrology and transplantation. 2013;6(1):45-50.
33. Torres IB, Moreso F, Sarró E, Meseguer A, Serón D. The interplay between inflammation and fibrosis in kidney transplantation. BioMed research international. 2014;2014.
34. Li L, Okusa MD, editors. Macrophages, dendritic cells, and kidney ischemia-reperfusion injury. Seminars in nephrology; 2010: Elsevier.
35. Devarajan P. Update on mechanisms of ischemic acute kidney injury. Journal of the American Society of Nephrology. 2006;17(6):1503-20.
36. Zhang H, Li Z, Li W. M2 Macrophages Serve as Critical Executor of Innate Immunity in Chronic Allograft Rejection. Frontiers in Immunology. 2021;12.
37. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxidants & redox signaling. 2014;20(7):1126-67.
38. Ramesh G, Reeves WB. Inflammatory cytokines in acute renal failure. Kidney International. 2004;66:S56-S61.
39. Leach HG, Chrobak I, Han R, Trojanowska M. Endothelial cells recruit macrophages and contribute to a fibrotic milieu in bleomycin lung injury. American journal of respiratory cell and molecular biology. 2013;49(6):1093-101.
40. Sahin H, Wasmuth HE. Chemokines in tissue fibrosis. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2013;1832(7):1041-8.
41. Wynn TA, Barron L, editors. Macrophages: master regulators of inflammation and fibrosis. Seminars in liver disease; 2010: NIH Public Access.
42. Wermuth PJ, Jimenez SA. The significance of macrophage polarization subtypes for animal models of tissue fibrosis and human fibrotic diseases. Clinical and translational medicine. 2015;4(1):2.
43. Lee S, Huen S, Nishio H, Nishio S, Lee HK, Choi B-S, et al. Distinct macrophage phenotypes contribute to kidney injury and repair. Journal of the American Society of Nephrology. 2011;22(2):317-26.

44. Zarjou A, Yang S, Abraham E, Agarwal A, Liu G. Identification of a microRNA signature in renal fibrosis: role of miR-21. American Journal of Physiology-Renal Physiology. 2011;301(4):F793-F801.
45. Nikolic-Paterson DJ, Wang S, Lan HY. Macrophages promote renal fibrosis through direct and indirect mechanisms. Kidney International Supplements. 2014;4(1):34-8.
46. Chen S-Y, Tian S. Macrophage polarization in kidney diseases. Macrophage. 2015;2(1):10-14800/macrophage. 679.
47. Braga TT, Correa-Costa M, Guise YFS, Castoldi A, de Oliveira CD, Hyane MI, et al. MyD88 Signaling Pathway Is Involved in Renal Fibrosis by Favoring a T. Mol Med. 2012;18:1231-9.
48. Geng Y, Zhang L, Fu B, Zhang J, Hong Q, Hu J, et al. Mesenchymal stem cells ameliorate rhabdomyolysis-induced acute kidney injury via the activation of M2 macrophages. Stem Cell Res Ther. 2014;5(3):80.
49. Wise AF, Williams TM, Kiewiet MB, Payne NL, Siatskas C, Samuel CS, et al. Human mesenchymal stem cells alter macrophage phenotype and promote regeneration via homing to the kidney following ischemia-reperfusion injury. American Journal of Physiology-Renal Physiology. 2014;306(10):F1222-F35.
50. Li W, Zhang Q, Wang M, Wu H, Mao F, Zhang B, et al. Macrophages are involved in the protective role of human umbilical cord-derived stromal cells in renal ischemia–reperfusion injury. Stem cell research. 2013;10(3):405-16.
51. Sedrakyan S, Da Sacco S, Milanesi A, Shiri L, Petrosyan A, Varimezova R, et al. Injection of amniotic fluid stem cells delays progression of renal fibrosis. Journal of the American Society of Nephrology. 2012;23(4):661-73.
52. Pan B, Liu G, Jiang Z, Zheng D. Regulation of Renal Fibrosis by Macrophage Polarization. Cellular Physiology and Biochemistry. 2015;35(3):1062-9.
53. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nature reviews immunology. 2008;8(12):958-69.
54. Song E, Ouyang N, Hörbelt M, Antus B, Wang M, Exton MS. Influence of alternatively and classically activated macrophages on fibrogenic activities of human fibroblasts. Cellular immunology. 2000;204(1):19-28.
55. Mosser DM. The many faces of macrophage activation. Journal of leukocyte biology. 2003;73(2):209-12.
56. Vidal B, Serrano AL, Tjwa M, Suelves M, Ardite E, De Mori R, et al. Fibrinogen drives dystrophic muscle fibrosis via a TGFβ/alternative macrophage activation pathway. Genes & development. 2008;22(13):1747-52.
57. Foster W, Li Y, Usas A, Somogyi G, Huard J. Gamma interferon as an antifibrosis agent in skeletal muscle. Journal of orthopaedic research. 2003;21(5):798-804.
58. Shearer JD, Richards JR, Mills CD, Caldwell MD. Differential regulation of macrophage arginine metabolism: a proposed role in wound healing. American Journal of Physiology-Endocrinology And Metabolism. 1997;272(2):E181-E90.
59. Satriano J, Matsufuji S, Murakami Y, Lortie MJ, Schwartz D, Kelly CJ, et al. Agmatine suppresses proliferation by frameshift induction of antizyme and attenuation of cellular polyamine levels. Journal of Biological Chemistry. 1998;273(25):15313-6.
60. Schnoor M, Cullen P, Lorkowski J, Stolle K, Robenek H, Troyer D, et al. Production of type VI collagen by human macrophages: a new dimension in macrophage functional heterogeneity. The Journal of Immunology. 2008;180(8):5707-19.
61. Gratchev A, Guillot P, Hakiy N, Politz O, Orfanos C, Schledzewski K, et al. Alternatively Activated Macrophages Differentially Express Fibronectin and Its Splice Variants and the Extracellular Matrix Protein βIG-H3. Scandinavian journal of immunology. 2001;53(4):386-92.

62. Guo YS, Tang J, Chen B, Huang W, Li Y, Cui HY, et al. betaig-h3 regulates store-operated Ca2+ entry and promotes the invasion of human hepatocellular carcinoma cells. Cell biology international. 2011;35(8):811-7.
63. Kim H-J, Kim I-S. Transforming growth factor-β-induced gene product, as a novel ligand of integrin α M β 2, promotes monocytes adhesion, migration and chemotaxis. The international journal of biochemistry & cell biology. 2008;40(5):991-1004.
64. LeBaron RG, Bezverkov KI, Zimber MP, Pavelec R, Skonier J, Purchio A. βIG-H3, a novel secretory protein inducible by transforming growth factor-β, is present in normal skin and promotes the adhesion and spreading of dermal fibroblasts in vitro. Journal of Investigative Dermatology. 1995;104(5):844-9.
65. Nacu N, Luzina IG, Highsmith K, Lockatell V, Pochetuhen K, Cooper ZA, et al. Macrophages produce TGF-β-induced (β-ig-h3) following ingestion of apoptotic cells and regulate MMP14 levels and collagen turnover in fibroblasts. The Journal of Immunology. 2008;180(7):5036-44.
66. Schäffer M, Bongartz M, Hoffmann W, Viebahn R. Regulation of nitric oxide synthesis in wounds by IFN-γ depends on TNF-α. Investigative Surgery. 2006;19(6):371-9.
67. Takamiya M, Fujita S, Saigusa K, Aoki Y. Simultaneous detection of eight cytokines in human dermal wounds with a multiplex bead-based immunoassay for wound age estimation. International journal of legal medicine. 2008;122(2):143-8.
68. Anders H-J, Frink M, Linde Y, Banas B, Wörnle M, Cohen CD, et al. CC chemokine ligand 5/RANTES chemokine antagonists aggravate glomerulonephritis despite reduction of glomerular leukocyte infiltration. The Journal of Immunology. 2003;170(11):5658-66.
69. Yokoo T, Ohashi T, Utsunomiya Y, Kojima H, Imasawa T, Kogure T, et al. Prophylaxis of antibody-induced acute glomerulonephritis with genetically modified bone marrow-derived vehicle cells. Human gene therapy. 1999;10(16):2673-8.
70. Yang J, Reutzel-Selke A, Steier C, Jurisch A, Tullius SG, Sawitzki B, et al. Targeting of macrophage activity by adenovirus-mediated intragraft overexpression of TNFRp55-Ig, IL-12p40, and vIL-10 ameliorates adenovirus-mediated chronic graft injury, whereas stimulation of macrophages by overexpression of IFN-γ accelerates chronic graft injury in a rat renal allograft model. Journal of the American Society of Nephrology. 2003;14(1):214-25.
71. Nishida M, Okumura Y, Fujimoto S-i, Shiraishi I, Itoi T, Hamaoka K. Adoptive transfer of macrophages ameliorates renal fibrosis in mice. Biochemical and biophysical research communications. 2005;332(1):11-6.
72. Wang Y, Wang Y, Zheng G, Lee V, Ouyang L, Chang D, et al. Ex vivo programmed macrophages ameliorate experimental chronic inflammatory renal disease. Kidney international. 2007;72(3):290-9.
73. Wilson HM, Chettibi S, Jobin C, Walbaum D, Rees AJ, Kluth DC. Inhibition of macrophage nuclear factor-κB leads to a dominant anti-inflammatory phenotype that attenuates glomerular inflammation in vivo. The American journal of pathology. 2005;167(1):27-37.
74. Wilson HM, Stewart KN, Brown PA, Anegon I, Chettibi S, Rees AJ, et al. Bone-marrow-derived macrophages genetically modified to produce IL-10 reduce injury in experimental glomerulonephritis. Molecular Therapy. 2002;6(6):710-7.
75. Tajik N, Salari F, Ghods A, Hajilooi M, Radjabzadeh M, Mousavi T. Association between recipient ICAM-1 K469 allele and renal allograft acute rejection. International journal of immunogenetics. 2008;35(1):9-13.
76. Famulski K, Kayser D, Einecke G, Allanach K, Badr D, Venner J, et al. Alternative Macrophage Activation-Associated Transcripts in T-Cell-Mediated Rejection of Mouse Kidney Allografts. American Journal of Transplantation. 2010;10(3):490-7.
77. Sis B, Famulski K, Allanach K, Zhu LF, Halloran P. IFN-γ Prevents Early Perforin-Granzyme-Mediated Destruction of Kidney Allografts by Inducing Donor Class I Products in the Kidney. American Journal of Transplantation. 2007;7(10):2301-10.

78. Famulski K, Sis B, Billesberger L, Halloran P. Interferon-γ and Donor MHC Class I Control Alternative Macrophage Activation and Activin Expression in Rejecting Kidney Allografts: A Shift in the Th1-Th2 Paradigm. American Journal of Transplantation. 2008;8(3):547-56.
79. Dehmel S, Wang S, Schmidt C, Kiss E, Loewe RP, Chilla S, et al. Chemokine receptor Ccr5 deficiency induces alternative macrophage activation and improves long-term renal allograft outcome. European journal of immunology. 2010;40(1):267-78.
80. Noelia A, Castrillo A. Liver X receptors as regulators of macrophage inflammatory and metabolic pathways. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2011;1812(8):982-94.
81. Kiss E, Popovic Z, Bedke J, Wang S, Bonrouhi M, Gretz N, et al. Suppression of chronic damage in renal allografts by liver X receptor (LXR) activation: relevant contribution of macrophage LXRα. The American journal of pathology. 2011;179(1):92-103.
82. Tang PM-K, Nikolic-Paterson DJ, Lan H-Y. Macrophages: versatile players in renal inflammation and fibrosis. Nature Reviews Nephrology. 2019;15(3):144-58.
83. Özdemir BH, Özdemir FN, Demirhan B, Haberal M. TGF-β1 expression in renal allograft rejection and cyclosporine A toxicity. Transplantation. 2005;80(12):1681-5.
84. Ikezumi Y, Suzuki T, Yamada T, Hasegawa H, Kaneko U, Hara M, et al. Alternatively activated macrophages in the pathogenesis of chronic kidney allograft injury. Pediatric Nephrology. 2015;30(6):1007-17.
85. Zakrzewicz A, Atanasova S, Padberg W, Grau V. Monocytic Tissue Transglutaminase in a Rat Model for Reversible Acute Rejection and Chronic Renal Allograft Injury. Mediators of Inflammation. 2015;2015.
86. Otukesh H, Hoseini R, Rahimzadeh N, Hosseini S, Ahmadpoor P, Javadilarijani F. The Role of Ischemia Reperfusion Damage on Renal Transplant, what are the new treatments? Journal of Pediatric Nephrology. 2013;1(1):8-17.
87. Wise AF, Ricardo SD. Mesenchymal stem cells in kidney inflammation and repair. Nephrology. 2012;17(1):1-10.