

Macrophages polarization in renal inflammation and fibrosis animal models (Review)

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Abstract. Chronic kidney disease (CKD) is a significant public health concern. Renal fibrosis is the final common pathway in the progression of kidney diseases, irrespective of the initial injury. Substantial evidence underscores the pivotal role of renal inflammation in the genesis of renal fibrosis. The presence of macrophages within normal renal tissue is significantly increased within diseased renal tissue, indicative of their crucial regulatory function in inflammation and fibrosis. Macrophages manifest a high degree of heterogeneity, exhibiting distinct phenotypic and functional traits in response to diverse stimuli within the local microenvironment in various types of kidney diseases. Broadly, macrophages are categorized into two principal groups: Classically activated, designated as M1 macrophages and alternatively activated, designated as M2 macrophages. A number of experimental models are widely used to study the underlying mechanisms driving renal inflammation and fibrosis progression. The present review delineated the phenotypic and functional attributes of macrophages present in diverse induced models, analyzing their disposition in relation to M1 and M2 polarization states.

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Introduction

Chronic kidney disease (CKD) stands as a major public health concern (1), significantly affecting the quality of life of patients (2). Renal fibrosis is the final shared route of progressive kidney diseases, irrespective of the initial injury (3). Compelling evidence highlights the pivotal role of renal inflammation in the initiation and advancement of renal fibrosis, emphasizing the contemporary focus on CKD prevention in clinical practice.

The first recognized function of macrophages is infection clearance. They are highly heterogeneous cells essential to the body's immune system (4-6). Macrophages are ubiquitously distributed across nearly all tissues and are established during embryonic development (5,7). In mature individuals, macrophages originate from bone marrow-derived monocytes, circulating in the blood stream and continually homing to tissues, where they ultimately differentiate into macrophages. Macrophage infiltration constitutes a common feature of CKD, with the degree of invasion and the extent of kidney injury (8).

Macrophages play a critical role in the progressive trajectory of renal fibrosis, with previous studies emphasizing their role in the clearance of dead cells and debris (characteristic function of M1 macrophages). In addition to M1 macrophages, M2 macrophages contribute to humoral immunity and tissue repair (7-9). Mounting evidence suggests that the ultimate outcome of renal disease is substantially influenced by the functional diversity stemming from alterations in macrophage phenotype. Studies have underscored that the polarization of macrophages holds the key to understanding kidney injury, including renal inflammation and fibrosis (7-9).

2. Macrophage polarity

Macrophages are broadly categorized into two primary groups: The classically activated, or pro-inflammatory (M1) and the alternatively activated, or anti-inflammatory (M2) macrophages (10). M1 and M2 macrophages are distinguished by their surface markers, functions and secreted factors. The M1 phenotype is induced by signaling from TNF- α and IFN- γ and is characterized by surface markers including cluster of differentiation (CD)40, CD80, CD83, and CD86. By contrast, the M2 phenotype is driven by IL-4 and marked by surface

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markers including CD2-6, CD163 and CD206. Functionally, M1 macrophages secrete an array of pro-inflammatory cytokines such as TNF- α , IL-1 α , IL-1 β , IL-6, IL-12, IL-23 and cyclooxygenase-2 (COX-2), collectively fostering an inflammatory milieu (11). By contrast, M2 macrophages release anti-inflammatory cytokines such as IL-4, IL-13, IL-12, IL-10 and TGF- β , all of which exert anti-inflammatory effects (12).

The secretions of M1 macrophage exhibit the capacity to eliminate bacteria, viruses and malignant tumor cells. However, excessive immune responses may lead to chronic inflammation and inflammatory diseases (13), necessitating the precise regulation of M1 macrophage functionality (14,15). Conversely, M2 macrophages are involved in tissue repair and immune tolerance (16).

3. Macrophage polarity in chronic inflammation and renal fibrosis

Most instances of acute renal inflammation are concomitant with an infiltration of M1 macrophages. Although M1 macrophages are a key feature of chronic kidney inflammation, the infiltration of these macrophages' transitions to the M2 phenotype occurs during the chronic developmental stage of the disease. The emergence of renal fibrosis is the most reliable predictor of renal disease progression and macrophages are a common feature of active fiber lesions in the kidney; therefore, an increased number of macrophages is also a marker of the progression of renal fibrosis (7). Several recent studies have similarly emphasized the pivotal role of macrophage polarization driving the renal inflammation and fibrosis (9,17,18). A number of experimental models have been extensively employed to dissect the intricacies of the mechanisms underpinning the transition from renal disease to renal fibrosis (19,20). Given this perspective, the present review endeavors to scrutinize the role of macrophage polarization in different animal models of renal fibrosis.

Unilateral ureteral obstruction (UUO). The UUO model is the most widely employed interstitial fibrosis model due to its rapid development of tubular atrophy, interstitial fibrosis and matrix deposition (21). The UUO animal model and human obstructive nephropathies share similar etiological factors (22,23). Following complete UUO in the obstructed kidney, there is epithelial tubular cell damage (24), leading to a significant increase in renal fibrosis indicators such as inflammation mediated by macrophages (25,26) and myofibroblasts (24). M1 and M2 macrophages fulfill contrasting yet complementary roles in tissue fibrosis (27,28). Indeed, tubular epithelial cells are targeted for macrophage-induced apoptosis in the obstructed kidney (29). The process of apoptotic cell recognition and phagocytosis by macrophages facilitates their differentiation into M2 macrophages (27,30). M2 macrophages are prominent producers of TGF- β , capable of inducing myofibroblast proliferation (30,31). By contrast, M1 macrophages produce MMPs and can also induce myofibroblasts to produce MMPs that promote extracellular matrix (ECM) degradation and facilitate the resolution of fibrosis (9,31). Some data suggest that transfusion of legumain-overexpressing macrophages can alleviate UUO-induced renal fibrosis (32). Notably, macrophages of differing phenotypes can coexist, and they

may revert to a resting state (M0 macrophage) or be repolarized due to the influence of the kidney microenvironment (32). During the early stages of UUO, the interstitium is dominated by the M1 phenotype, whereas M2 macrophages accumulate at later stages (33). Additionally, studies have shown that mice lacking in IRAK-M, an inhibitor of pro-inflammatory cytokines expression in internal macrophages (34), are protected in experimental models of UUO-induced kidney injury, leading to reduced renal fibrosis and a lower number of M2 macrophages. Figueiredo *et al* (35) found that relaxin can suppress the typical M-cytokine IL-1 β expression in macrophages in response to inflammatory stimuli, thereby promoting the acquisition of an immunosuppressive M2 phenotype in macrophages. Consistent with earlier findings, relaxin can promote the acquisition of an immunosuppressive M2 phenotype. M2 macrophages mitigate kidney inflammation by releasing anti-inflammatory mediators, such as IL-10, which inhibit renal fibrosis (9,35-37). Relaxin, acting as a swift yet safe anti-fibrotic agent, inhibits renal fibrosis in UUO (38-40). Studies have demonstrated the potential of relaxin to shift macrophage polarization towards the M2 phenotype (40,41). The microenvironment may induce macrophage polarization (42). Studies have suggested that complement proteins may influence macrophage phenotypes (43,44). Although the complement proteins affect macrophage polarization (43,44), whether complement component 3 (C3) can induce macrophage polarization and regulate renal fibrosis remains uncertain. Recent data demonstrate a close correlation between interstitial infiltrating macrophages and C3-expressing renal tubules in UUO mice (44). C3 deficiency facilitates the shift of infiltrating macrophage toward the M2 phenotype during the early stage of UUO (44) (Fig. 1). In summary, while these have limitations, they offer new insights for future therapeutic approaches to renal fibrosis treatment (44).

Aldosterone and mineralocorticoid receptor (MR). Studies have unequivocally established the pivotal role of macrophages in renal inflammation, fibrosis and the remodeling induced by MR (45,46). Although heightened macrophage infiltration has been reported previously in a rat model administered aldosterone and salt (46), the precise macrophage phenotype responsible remains somewhat elusive. The present study identified that in the MR model, it mainly mediated the M1 phenotype (5,42). Preceding the onset of fibrosis, aldosterone triggers the infiltration of monocytes and macrophages, alongside an elevated expression of inflammatory markers such as COX-2, monocyte chemoattractant protein1 and intercellular adhesion molecule 1 in the heart, vasculature and kidney (46). Studies have demonstrated the significance of aldosterone in the inflammatory and fibrotic processes in kidney diseases, wherein the aldosterone-induced enhancement of renal lesions frequently coincides with a marked inflammatory response, primarily involving macrophage-released inflammatory factors during renal fibrosis (47,48). In recent years, the influence of complement proteins on macrophage phenotypes has emerged. For example, DOCA-salt hypertensive mice that received bone marrow from knockout mice exhibited lower M1 and higher M2 macrophage count within perivascular adipose tissue, thereby concomitantly ameliorating vascular injury in contrast to mice receiving bone marrow from wild-type

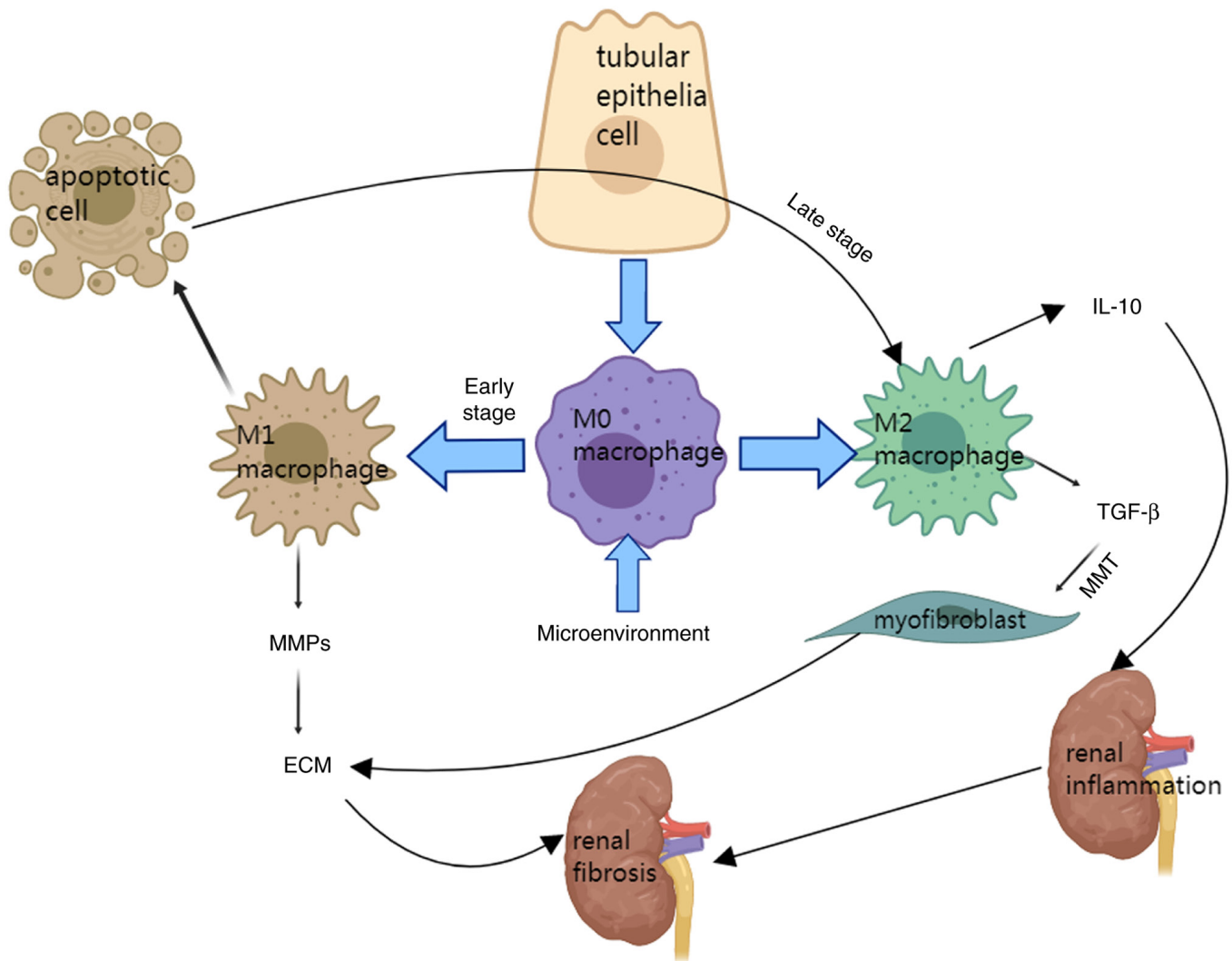


Figure 1. In the early stage of the UUO model, the interstitium is mainly M1 phenotype, producing matrix metalloproteinases, which can induce the production of MMP in myofibroblasts, promote the degradation of ECM, and promote the dissolution of fibrosis. However, at the late stage, M2 macrophages begin to accumulate, and M2 macrophages are the main producers of TGF- β , able to induce myofibroblast proliferation. Macrophages reduce inflammation through the uptake of apoptotic cells or exposure to anti-inflammatory cytokines such as IL-10 and TGF- β and exhibit pro-fibrotic properties, promoting tissue remodeling in which high ECM deposition predominates. UUO, unilateral ureteral obstruction; ECM, extracellular matrix.

mice (44). Nevertheless, macrophage phenotypes should not be simplistically confined to M1 and M2 classifications, as substantial heterogeneity exists within the kidney macrophage population both in healthy and injured kidneys (12). Furthermore, there exists evidence supporting the potential of MR aldosterone antagonist MRA to diminish renal inflammation and fibrosis (49). The use of specific aldosterone synthase inhibitors or aldosterone synthase-deficient mice has demonstrated efficacy in mitigating the progression of inflammation and fibrosis (50-52). Plasminogen activator inhibitor1 (PAI-1), a typical mediator of fibrosis, directly inhibits both tissue plasminogen activator and urokinase. The anti-inflammatory and anti-fibrotic effects of aldosterone could potentially arise through MR activation, fostering the expression of PAI-1 in multiple tissues, including the kidney (45). Within the kidney, aldosterone triggers PAI-1 expression via MR activation in podocytes, macrophages, mesangial cells and tubular epithelial cells (53,54). However, the clinical viability of PAI-1 inhibitors remains challenging to attain due to their limited

selectivity and notable toxicity (55). In addition to PAI-1, aldosterone may also instigate the activation of cytokines such as TGF- β , NF- κ B and IL-6 (54,56), which in turn might foster fibrosis development by recruiting inflammatory cells or promoting M1 macrophage polarization (53,57). Thus, MR targeting holds potential for modulating the balance between M1 and M2 phenotypes, directly influencing macrophages, or altering epithelial intercommunication, thereby delaying the onset of renal fibrosis and the development of CKD (58). Research indicates that after three weeks of aldosterone and a high-sodium diet, the expression of M1 surface markers in the kidney increased, a response that is counteracted by the addition of spironolactone. Conversely, other experiments have demonstrated that treatment with chlorophosphate solely diminishes M1 macrophage count without affecting M2 macrophage (Fig. 2). Therefore, the pro-inflammatory and pro-fibrotic consequences initiated by aldosterone can be mitigated by incorporating MR antagonists into macrophages (59). Nevertheless, the precise mechanism by which aldosterone

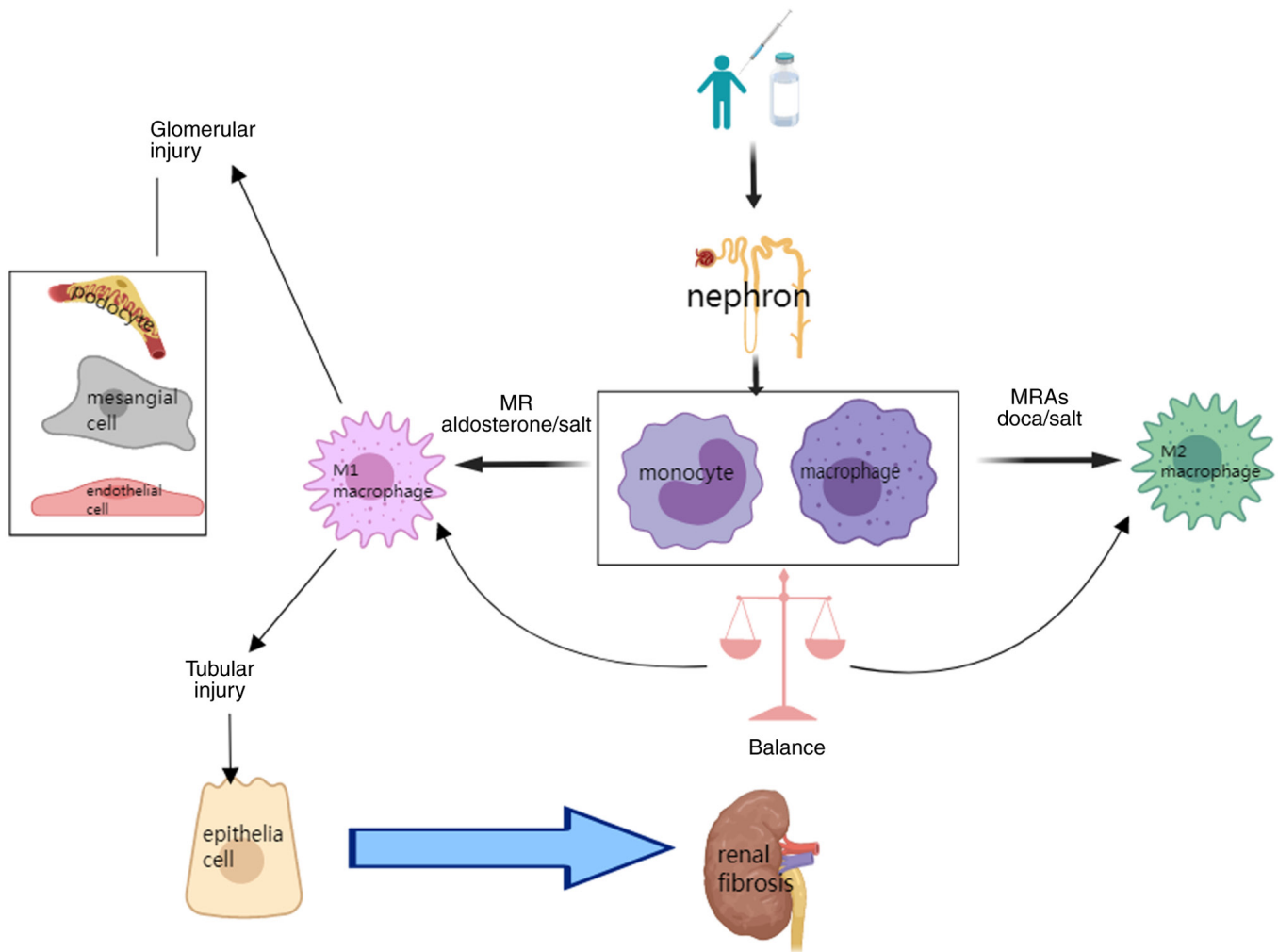


Figure 2. Macrophages polarized in MR model. Activation of the MR in monocytes/macrophages propels the direct transition from the M1 phenotype to the M2 phenotype, culminating in heightened renal fibrosis. Manipulating the MR presents a prospective avenue to mitigate renal fibrosis and hinder the progression of CKD by orchestrating a shift in the equilibrium between M1 and M2 macrophages. This can be achieved either through direct modulation of macrophages or by altering the crosstalk involving epithelial cells. MR, mineralocorticoid receptor; CKD, chronic kidney disease; MRA, aldosterone antagonist.

influences macrophages and fosters macrophage polarization remains incompletely elucidated *in vivo* (59).

Cisplatin (CDDP)-induced renal fibrosis. CDDP is a potent anticancer drug, yet it bears significant renal adverse effects (60-63). Various models of renal fibrosis induced by CDDP have been used (64-66). Macrophages constitute pivotal actors within several aspects of these processes, encompassing immune responses, wound healing and tissue remodeling. M1 macrophages swiftly emerge in the kidney following injury and are recognized as proinflammatory entities. Conversely, M2 macrophages manifest later in kidney injury and exhibit a phenotype conducive to tissue repair and anti-inflammatory functions. Although M1 macrophages may persist even in chronic injury, the transition from the M1 to the M2 phenotype is associated with the development of renal fibrosis (7,67). Sears *et al* (68) revealed that clodrosome diminished the number of F4/80^{hi} renal resident and M2 macrophages following small doses of cisplatin treatment but had no effect on F4/80^{lo} infiltrating macrophages in the kidney. This depletion was accompanied by reduced renal fibrosis following small doses of cisplatin treatment. By contrast,

Ccr2^{-/-} mice exhibit a reduced number of F4/80^{lo} infiltrating macrophages in the kidney following small doses of cisplatin treatment, with no effect on the accumulation of F4/80^{hi} renal resident or M2 macrophages. Moreover, the genetic knockout of Ccr2 has no bearing on the development of fibrosis following small doses of cisplatin treatment. In this study, clodrosome exhibited protective effects against the reduction of the number of F4/80^{hi} resident and M2 macrophages (68). Although recent studies undeniably emphasize the significant role played by macrophage polarization in the development of fibrotic diseases, uncertainties persist regarding whether macrophage polarization carries equivalent importance within an experimental model of renal fibrosis induced by CDDP (68,69). When endothelial cells from CDDP-treated entities were co-cultured with Raw264.7, mRNA expression levels of Arg-1 and CD206 were observed to be significantly increased. In contrast to other models, this outcome suggests that cisplatin might induce M2 macrophage polarization through the inflammatory milieu triggered by endothelial cells (69). Yu *et al* (69) demonstrated that cisplatin-induced an incomplete epithelial mesenchymal transition (EMT) within tubular epithelial cells (ECs), yet co-culturing cisplatin-treated

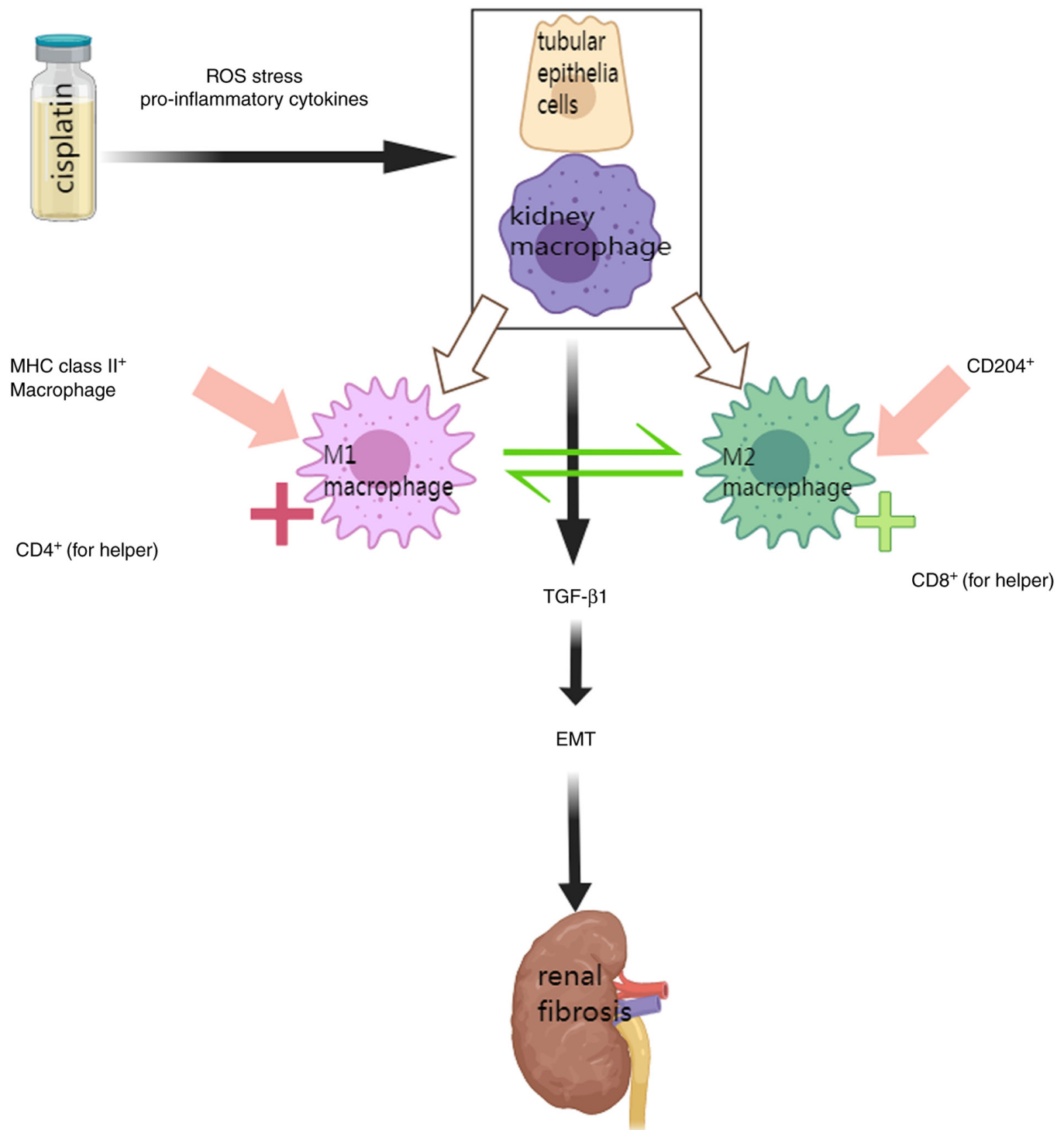


Figure 3. Macrophage polarization in the CDDP model. Cisplatin-induced nephrotoxicity culminates in the apoptosis of tubular ECs and tubulointerstitial fibrosis through the interplay of ROS stress and inflammatory cytokines. The emergence of renal fibrosis in response to cisplatin appears to be mediated by the activation of resident fibroblasts and the process of EMT within tubular ECs. Notably, cisplatin establishes an inflammatory milieu facilitated by tubular ECs, thus triggering the activation of fibroblasts and promoting M2 macrophage polarization. M2 macrophages can reciprocally facilitate the EMT process within cisplatin-treated ECs. In conclusion, the polarization of macrophages assumes a critical role in renal fibrosis induced by CDDP. CDDP, cisplatin; ECs, epithelial cells; ROS, reactive oxygen species; EMT, epithelial mesenchymal transition; CD, cluster of differentiation.

ECs with M2 macrophages, rather than M1, resulted in complete EMT. Furthermore, they found that co-culturing with cisplatin-treated tubular ECs spurred fibroblast activation and promoted M2 macrophage polarization. Generally, the M1 and M2 macrophages are liable to transformation, albeit this alteration does not uniformly affect the functional transition of

macrophages. For *in vivo* experiments, immunohistochemical methods employed for discerning M1 and M2 macrophages assume pivotal significance. One particular study used immunohistology techniques employing antibodies targeting cell surface molecules of macrophages within a CDDP-induced renal fibrosis model (70). In the CDDP-induced renal fibrosis

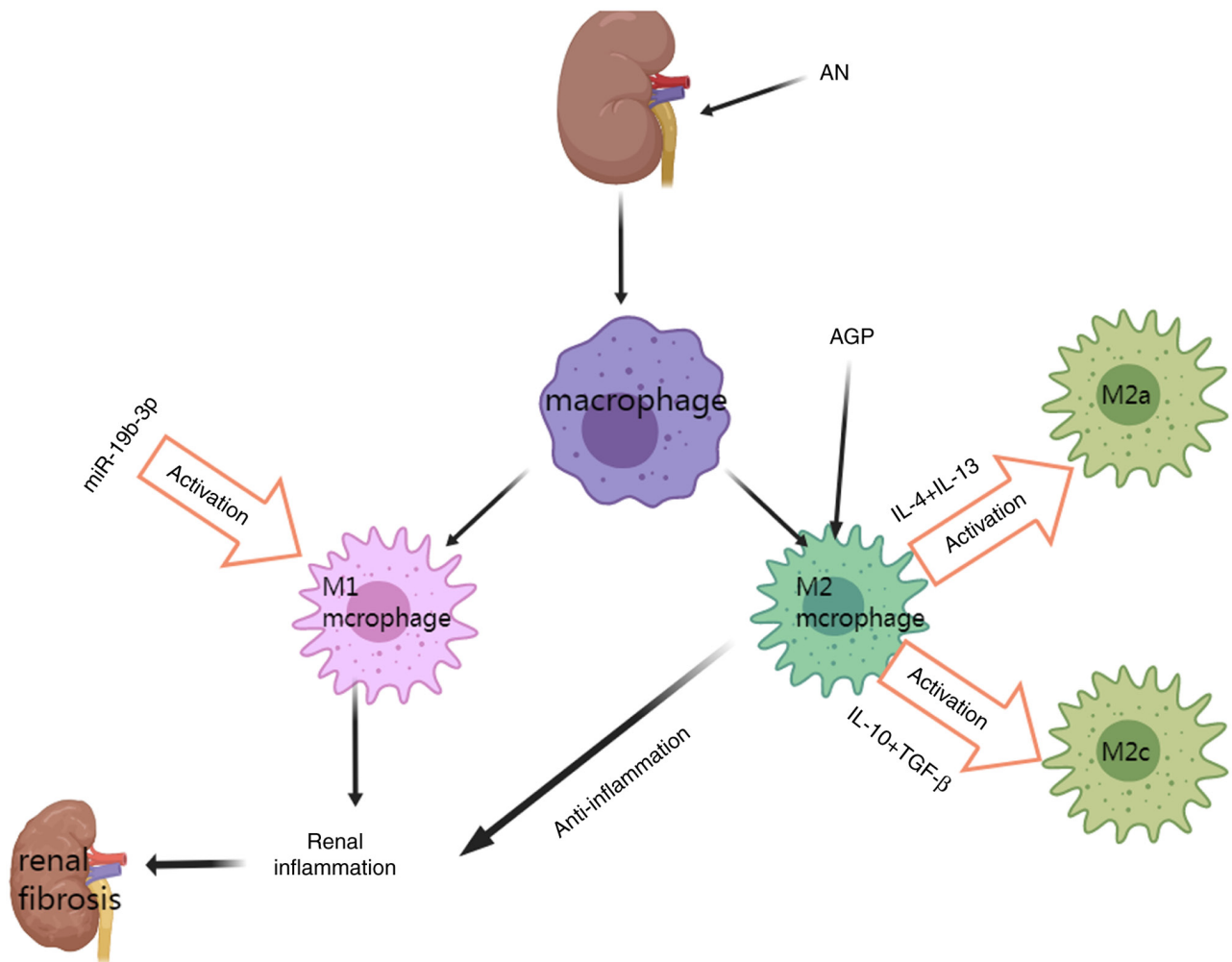


Figure 4. Macrophage polarization in ADR models. Different types of macrophages that were *in vitro* polarized into the M2 phenotype was adoptively transferred to mice with ADR-induced nephropathy. Among these, spleen-derived macrophages maintained the M2 phenotype in mice with ADR-induced nephropathy, but bone marrow-derived macrophages exhibited value-dependent phenotype switching and did not protect kidney, suggesting substantial plasticity of bone marrow-derived macrophages. Furthermore, the interplay between TECs and macrophages, mediated by miR-19b-3p is instrumental in the activation of M1 macrophages. In conclusion, the regulation of macrophage phenotypes in the renal milieu holds the potential to significantly curtail renal inflammation and fibrosis in the AN-induced renal fibrosis models. ADR, Adriamycin; TECs, tubular epithelial cells; miR, microRNA; AN, ADR nephropathy; AGP, α 1-acid glycoprotein.

model, the differently polarized macrophages may enact distinct roles at different stages of the disease course. M1 macrophages appearing primarily at mid-stage may participate in the progressive renal injury caused initially by CDDP. Notably, the number of M2 macrophages began to increase on day 5 and continued to increase until day 20. Similar to M2 macrophages, the levels of TGF- β 1 also increased from day 7 to day 20. Therefore, the findings of this study (71) indicate that the intermediate and late progressive renal fibrosis from day 9 to day 20 may be associated with the increase in the number of M2 macrophages and the levels of TGF- β 1 (70-72). Cisplatin-elicited reactive oxygen species (ROS) stress within compromised epithelial cells, coupled with the secretion of pro-inflammatory cytokines by neighboring immune cells, is a plausible etiology for EMT (Fig. 3). Macrophages emerge as pivotal players in the immunological milieu during both the inflammatory and recovery phases (73-75). However, the exact roles that macrophages assume in cisplatin induced EMT remain to be elucidated. Antecedently, it has been reported that phenotypes of M1 and M2 macrophages can fluidly

transition contingent upon the microenvironment (42,76,77). The intricate orchestration of progressive fibrosis might stem from the intricate interplay between M1 and M2 macrophages interacting with T cells encompassing CD4 (for helper functions) and CD8 (for cytotoxicity) (78). Taken together, it may be concluded that macrophage polarization has a significant impact on CDDP-induced renal fibrosis models.

Macrophages in Adriamycin (ADR)-induced nephropathy. ADR (doxorubicin) belongs to the anthracycline class of anti-tumor drugs, known for their broad spectrum of activity against human cancers (79). ADR nephropathy (AN) serves as a rodent model for CKD and has been extensively studied, enhancing our comprehension of the mechanisms underlying the progression of chronic proteinuric renal disease (79). AN is characterized by podocyte injury, subsequent glomerulosclerosis, tubulointerstitial inflammation and fibrosis (79). In rats, ADR-induced nephropathy results in substantial proteinuria and tubular basement membrane lesions, potentially provoking an inflammatory response and interstitial fibrosis (80). AN

boasts several strengths as an experimental model of kidney disease. Its renal injury induction is highly reproducible and exhibits robustness with severe tissue injury yet acceptable mortality (<5%) and morbidity (weight loss). As renal injury occurs within a few days of drug administration, the temporal occurrence of injury is consistent and predictable. Nonetheless, the model also has some limitations, as different AN batches may induce varying degrees of kidney injury (81). Research has highlighted the efficacy of M2 macrophages induced by IL-4 or IL-4/IL-13 administration against renal injury resulting from ADR-induced nephropathy in mice (67,82). These studies suggest that regulation of macrophage phenotypes in the kidney could play a pivotal role in reducing renal inflammation and proteinuria. Recent clinical studies have underscored the critical influence of proteinuria on the progression of CKD and the onset of cardiovascular disease. Inflammation and macrophage infiltration into renal tissue have been implicated as contributing factors to proteinuria. α_1 -acid glycoprotein (AGP), an acute-phase plasma protein, leaks into the urine in patients with proteinuria (81,82). One study found that AGP potentiates the shift of macrophage phenotype towards CD163-expressing macrophages with anti-inflammatory functions *in vivo*, thereby mitigating proteinuria, inflammation and renal damage (83).

In general, M2-type macrophages can be further divided into four subtypes: M2a, M2b, M2c and M2d. Previous studies have elucidated the transfer of macrophages polarized by exposure to IL-4 and IL-13, thereby attaining an M2a phenotype, as an efficacious intervention for countering ADR-induced nephropathy in severe combined immunodeficient mice (82-84). Furthermore, the infusion of macrophages that have been *ex vivo* modified into M2c phenotypes through exposure to IL-10 and TGF- β has been shown to furnish protection against renal injury in AN (82). These findings collectively propose the *ex vivo* manipulation of macrophages to adopt M2 phenotypes as a promising therapeutic avenue for managing chronic inflammatory renal disease (82). However, the specific distinctions, if any, between the protective capabilities of M2a and M2c phenotypes against renal injury, remain unexplored, as do potential variations in the underlying mechanisms that substantiate the protective effects of these two distinct types of M2 macrophages. Cao *et al* (85,86) has extensively investigated the ramifications of introducing *in vitro*-generated M2 macrophages into rodent models, encompassing scenarios of acute kidney failure and CKD (82). Using a mouse model of AN, the investigation of Cao *et al* (85,86) showed that a solitary intravenous infusion of 1×10^6 macrophages generated from splenic CD116⁺ cells and exposed to M2c macrophage polarization, exhibited heightened protective efficacy against kidney injury compared to M2a macrophages (85). These M2c macrophages are capable of exhibiting elevated expression levels of B7-H4, a member of the B7 family (87). This protein is recognized for its capacity to curtail T cell proliferation and induce regulatory T cells, as substantiated both *in vivo* and *in vitro*. It should be noted, however, that despite undergoing some alteration in phenotype during the disease course, these M2c macrophages did not undergo a complete transformation towards the M1 phenotype (85,88). Furthermore, an alternative facet of the research demonstrated that M2 macrophages originating from the spleen (SP-M2) were associated with

enhanced kidney injury mitigation within the AN model of severe combined immunodeficiency (SCID) mice (82). By contrast, some other findings (86) indicate that the utilization of bone marrow-derived M2 macrophages (BM-M2) does not confer protection to renal tissue or function within the same model. Therefore, these findings collectively suggest that in the AN experimental model involving SCID mice, the inhibitory function of BM-M2 may wane *in vivo* due to its proliferative effects, while SP-M2 proves protective as a result of its non-proliferative nature. The transfer of SP-M2 phenotypes appears to promote renal fibrosis (86,89). Similar to various tissues, recent investigations have also elucidated that an experimental model of doxorubicin-induced cardiotoxicity (Dox-induced cardiotoxicity) may entail the infiltration of M1 macrophages, thereby inciting inflammation and fibrosis (90,91). Exosomes (cell-derived vesicles) enhance M2 macrophages in Dox-induced cardiotoxicity model (90,92,93), a trend congruent with prior literature (94-97). Immune cells are capable of internalizing exosomal miRNAs, thereby orchestrating the regulation of inflammatory responses, as previously reported (98). A mounting body of evidence further underscores the pivotal role of miRNAs in the progression of both kidney disease and inflammatory disease (99,100). This exosome-mediated inflammatory pathway introduces a novel mechanism underpinning the development of renal inflammation by facilitating communication between Tubular Epithelia Cells and macrophages. Indeed, a study demonstrated the mediation of crosstalk between TECs and macrophages through exosomal miR-19b-3p, which contributes to M1 macrophage activation (101) (Fig. 4). The findings suggest that exosomal miR-19b-3p could potentially emerge as a promising therapeutic target for the advancement of kidney disease mitigation (101). In light of the aforementioned, the precise regulation of macrophage phenotypes within the renal context emerges as a pivotal strategy for curbing renal inflammation and fibrosis in AN-induced renal fibrosis models.

Ischemia reperfusion injury (IRI) renal fibrosis. Renal IRI refers to the damage that arises from the interruption and subsequent restoration of blood flow to the kidney. The hypoxia that ensues upon IRI leads to irreversible damage to tubular cells in the S3 segment of nephrons and an exacerbated innate immune response, commonly referred to as necroinflammation (102). IRI stands out as one of the most crucial pathological process contributing to acute kidney injury (AKI) (103). The pathogenesis of renal fibrosis in IRI has been attributed to a number of factors, including inflammatory cell infiltration, the production of proinflammatory chemokines and cytokines, recruitment of bone marrow-derived fibroblasts and accumulation of M2 macrophages (104,105). Interferon regulatory factor 4 (IRF4) functions as a suppressor of innate immune signaling, by inhibiting Toll-like receptor/myeloid differentiation primary response 88 signaling (TLR/MyD88 signaling) (106). In the acute phase of IRI, IRF4 serves as an endogenous regulator of myeloid cell activation such as dendritic cells, restraining the release of TNF- α release from intrarenal myeloid cells and thereby limiting tubular cell necrosis, tissue inflammation and acute renal failure 24 h and 5 days post-IRI (107). Several studies have shown that M1 macrophage-driven chronic renal inflammation accelerates renal fibrosis formation and the

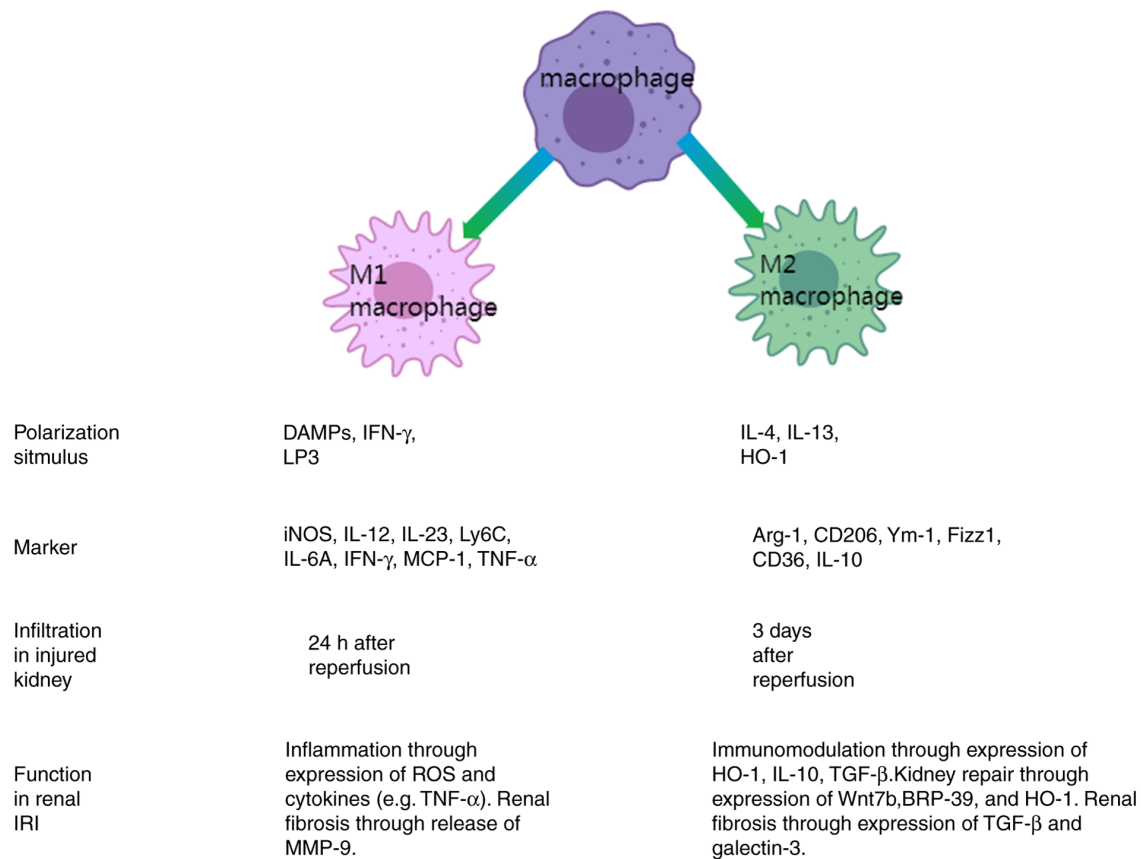


Figure 5. Macrophage polarization in IRI model. M1 macrophages exhibited infiltration 24 h after kidney reperfusion and caused kidney injury. However, 3 days after reperfusion, M2 macrophages could be detected in the kidneys. Macrophages resident in renal tissues exhibit a propensity for differentiation into distinct subsets, driven by fluctuations in the local microenvironment. M1 macrophages may participate in inflammatory responses through the secretion of cytokines and ROS and may also promote renal fibrosis through the release of MMP-9. M2 macrophages may mediate kidney repair through the secretion of Wnt7b, BRP-39 and HO-1, but may also induce renal fibrosis, perhaps through the release of galectin-3 and TGF- β . IRI, ischemia reperfusion injury; ROS, reactive oxygen species; HO-1, heme oxygenase-1; BRP-39, breast regression protein 39.

progression of CKD in IRI models (107,108). The essential role of IL-4 and IL-13 as determinants for M2 macrophage activation is well-established (76). Therefore, certain findings indicate that IL-18 could inhibit the expression of macrophage M2 surface marker. As M2 macrophages have long been associated with the pathogenesis of renal fibrosis, inhibiting IL-18 in IRI-induced renal fibrosis, may impede macrophage M2 polarization, thereby accelerating the development of renal fibrosis (109). Emerging evidence underscores that macrophages can directly contribute to a fibrotic response through transitioning into myofibroblasts, a phenomenon termed macrophage-myofibroblast transition (MMT) (89,110). The MMT process introduces a novel mechanism for myofibroblast formation and the development of renal fibrosis (75). In a specific study, IL-18 treatment significantly decreases the number of CD206+ and α -SMA+ cells in the kidneys of mice following IRI. These findings suggest that the inhibition of IL-8 reduces the progression of renal fibrosis by suppressing the transition of M2 macrophages to myofibroblasts (109).

Previous studies have shown that STAT1 activation is increased in primary cardiac myocytes following IRI (111). Other studies have shown that STAT1 modulates autophagy and regulates both cardioprotective and harmful effects of STAT1 in heart injury (111,112). Various studies have emphasized the role of alternatively activated M2-like macrophages

in renal fibrosis (104,113). Although these so-called M2-like macrophages are capable of generating numerous profibrotic mediators, their ability to support host defense mechanisms is limited (114). Some investigations have showed that renal fibrosis is not only a result of persistent inflammation, but also activated macrophages and genetic factors that determine long-term outcomes of IRI (115). The IFN- γ /STAT1 pathway has been suggested to play a crucial role in the development of classically activated macrophages and that this is regulated via different mechanisms. In conclusion, STAT1 deficiency in mice enhances renal fibrosis following renal IRI. Studies *in vitro* on macrophages differentiation suggest that STAT1-insufficiency dependent predominance of alternatively activated macrophages may be responsible for renal tissue remodeling (111,112,116).

Previous reports indicate that P144 (TGF- β 1 inhibitory peptide) can impede the progression of liver fibrosis (117,118) and myocardial fibrosis (119). TGF- β 1 has been shown to reduce fibroblast activation and collagen deposition *in vivo* in animal models of kidney disease (120). In IRI, macrophage is the primary infiltrating immune cells in the kidney tissue. Thus, it is reasonable to hypothesize that macrophages may operate downstream of TGF- β 1 in a model of renal fibrosis induced by IRI (121). Moreover, the progression of renal fibrosis after IRI has been strongly associated with an increased

number of M2 macrophages (7). In addition, TGF- β 1 has the capacity to induce macrophages polarization toward the M2 phenotype (104). The introduction of P144 significantly prevents the upregulation of CD206, indicating reduced M2 polarization (121). P144 not only prevents M2 macrophage polarization but also curtails the phosphorylation of Smad3 at both the transcriptional and translational levels. Thus, P144 has a substantial inhibitory effect on M2 macrophage infiltration in renal tissue (121).

Studies have shown that prior to the occurrence of AKI, macrophages are depleted, resulting in a protective effect on the kidney. The phenotypic alterations of macrophages are dynamic (122,123). However, other studies have presented evidence of the presence of M2 macrophages in injured kidneys, which could potentially lead to the secretion of fibrotic growth factors and promote extracellular matrix production (76,68,123). One study indicates that IKK α could contribute to macrophage M2 polarization. Depletion of IKK α in macrophages resulted in reduce M2 polarization and kidney fibrosis after IRI (123). Given that macrophage phenotype determines their function as well as the development of CKD, the researchers examined macrophage polarization following inflammatory stimulation. It was concluded that IKK α -dependent noncanonical NF- κ B pathway activation facilitates macrophage M2 polarization, which in turn triggers cytokine-mediated activation of the Wnt/ β -catenin pathway, ultimately leading to fibrosis in the injured kidney (123). The role of M2 macrophages encompasses not only anti-inflammatory functions but also pro-fibrotic attributes, notably within the context of kidney IRI. Notably, certain AKI biomarkers, such as neutrophil gelatinase-associated lipocalin and monocyte chemotactic protein-1, exhibit associations with fibrosis following AKI, within the rat bilateral IRI model. Notably, M2 macrophage, rather than M1, infiltration into the kidney demonstrated a significant association with the degree of fibrosis. Alternatively, the study proposed that suppressing M2 macrophage infiltration during the chronic phase after AKI might hold potential for preventing fibrosis progression, warranting further investigation (124).

In kidney tissue, different subsets of macrophages may exist, and macrophages may switch between phenotypes depending on the microenvironment (67). Thus, M1 macrophages further exacerbate AKI caused by IRI by releasing pro-inflammatory cytokines (67,125). Alternatively, other studies indicate that M1 macrophages also contribute to recruiting neutrophils to induce epithelial cell apoptosis (126). In addition to exerting strong pro-inflammatory effects, M1 macrophages can either promote or amplify Th1 polarization in CD4+T cells by releasing IL-12 (127). However, M2 macrophages reduce kidney inflammation by secreting anti-inflammatory cytokines (127). Furthermore, M2 macrophages may also release galectin 3, which induces renal fibrosis (128). Several studies have highlighted that MMT cells that directly lead to fibrogenesis may predominantly have a M2 phenotype (91,105,129). Altogether, M1 and M2 macrophages may promote renal fibrosis through both direct and indirect pathways. In 2009, Weis *et al* (130) first described the involvement of the hemoxygenase-1 (HO-1) cytoprotective pathway in the polarization of macrophages toward the M2 phenotype. Studies have also shown that HO-1 also regulates macrophage polarization and

prevents damage induced by hepatic IRI through the polarization of the M2 phenotype (130-132). HO-1 can facilitate a microenvironment that favors the transition from macrophages to M2 phenotype, effectively alleviating AKI damage, preventing the transition to CKD and promoting kidney tissue repair following injury (132). Several studies have reported that MCP1 inhibits M1 polarization by blocking NF- κ B. The findings suggest that MCP1 deficiency can promote M2 macrophage polarization through IRF4 (133,134).

Inflammation plays a pivotal role in the pathogenesis of renal IRI (135,136). During the recovery phase of IRI, macrophages of the M2 phenotype constitute the prevailing subset. Despite M2 macrophages being crucial for short-term recovery, they are also implicated in the development of renal fibrosis subsequent to IRI. To conclude, M2 macrophages play a significant role in fibrosis progression during the transition, from AKI to CKD, with their actions at least partially contingent upon TGF- β (Fig. 5). Thus, when macrophages are regarded as therapeutic targets or tools in the progression from AKI-to-CKD, a more nuanced understanding of achieving an optimal balance between M1 and M2 macrophages to promote recovery while reducing fibrosis is essential for the formulation of clinically viable strategies to impede CKD progression (104).

Folic acid (FA)-mediated renal fibrosis. The progression of CKD following AKI is characterized by robust inflammation and fibrogenesis (137). The rodent model of FA-induced nephropathy simulates essential aspects of the AKI-CKD transition. In the early phase, the pathogenesis of FA nephropathy is characterized by acute tubular cell necrosis and an inflammation response. Persistent inflammatory cell infiltration and fibrosis are two main pathological changes in the chronic phase of AKI. The effectiveness and feasibility of inducing kidney injury by FA treatment have been experimentally validated. Therefore, FA-induced renal fibrosis is considered an ideal model for studying the transition of AKI to CKD (138). A few studies have highlighted the substantial contribution of myeloid myofibroblasts and the transition of M2 macrophages to myofibroblasts in kidney fibrosis observed in FA nephropathy and chronic renal allograft injury (110,138). Previous findings have revealed that IL-4/STAT6 signaling exerts a crucial effect in FA-induced renal fibrosis by modulating bone marrow-derived fibroblasts activation and macrophage M2 polarization (111,112). Robust evidence supports IRF-4 as a downstream effector of the IL-4/STAT6 signaling pathway, driving the differentiation of bone marrow-derived monocytes into the M2 phenotype (139-141). Moreover, IRF-4 has been identified as a critical player in myeloid cells differentiation (142), macrophage activation (143) and inflammatory diseases (108). IRF-4 deficiency has been shown to suppress the inflammatory response, activation of the bone marrow-derived fibroblasts and the transition of macrophages to myofibroblasts in FA nephropathy (144).

MicroRNAs (miRs) regulate gene expression during various developmental stages of macrophages, including myelopoiesis, polarization and functional effects. In addition, miRs can also play a role in regulating the signaling and metabolic functions of macrophage polarization (145,146). In co-cultures of SOCS1 with human kidney 2 (HK-2 cells)

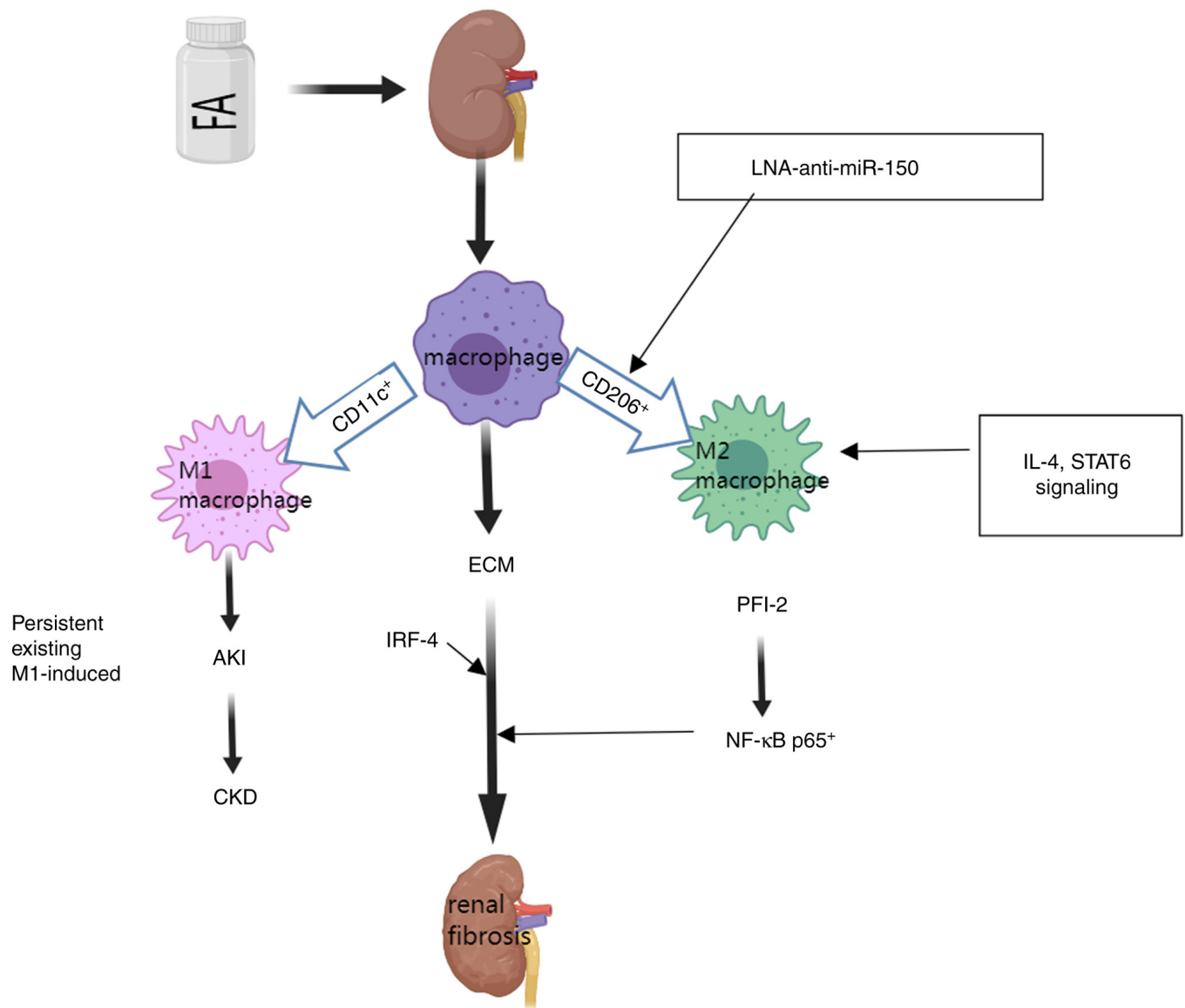


Figure 6. Macrophage polarization in fibrotic models induced by FA. Renal fibrosis is characterized by the excessive deposition of ECM and often accompanied by tubular atrophy. One of the most causes of renal fibrosis is intrarenal inflammation. Renal fibrosis is a complex process that involves multiple molecular signaling and multiple cellular components. In renal interstitial fibrosis with marked inflammation, macrophages assume a significant role as key actors. The IL-4/STAT6 signaling axis holds pivotal sway in FA-induced renal fibrosis, orchestrating the activation of bone marrow-derived fibroblasts and the polarization of macrophages toward the M2 phenotype. Forging a therapeutic path, LNA-anti-miR-150 emerges as an agent that mitigates renal fibrosis, predominantly through diminishing M1 macrophage prevalence and increasing M2 macrophage polarization. Additionally, SETD7 contributes to the inflammation responses in FA nephropathy operated by modulating NF-κB signaling. Thus, M1 and M2 macrophages undertake a distinct role within the matrix of FA-induced renal fibrosis models. FA, folic acid; ECM, extracellular matrix; LNA, locked nucleic acid; SETD7, SET domain-containing lysine methyltransferase 7; CD, cluster of differentiation; CKD, chronic kidney disease; miR, microRNA.

and macrophages, the antagonism of miR-150 by locked nucleic acid (LNA)-anti-miR-150 resulted in the reversal of the JAK/STAT pathway. These findings further support the notion that LNA-anti-miR-150 reduces FA-induced renal fibrosis (147,148). In an experimental model of FA-induced renal fibrosis, macrophage numbers were significantly elevated (149). Dysregulated macrophage polarization may contribute to a crucial mechanism in the progression of chronic renal inflammation and fibrosis. M1 macrophages might not only contribute to AKI in the early stages of the disease, but also may potentially drive renal fibrosis in later stages due to the sustained detrimental effects of M1 macrophages (149-151). One study (141) investigated the effects of a

selective STAT6 inhibitor, AS1517499, on myeloid fibroblast activation, macrophage polarization and the development of renal fibrosis in a murine mouse model of FA-induced nephropathy. The findings revealed that within the injured kidney tissue, STAT6 signaling becomes activated, leading to the aggregation and activation of myeloid fibroblasts as well as the polarization of M2 macrophages, ultimately culminating in the progression of renal fibrotic disease. Pharmacological inhibition of STAT6 with AS1517499 resulted in the suppression of myeloid fibroblast accumulation and activation, reduction in M2 macrophage polarization, decreased production of ECM proteins and attenuation of kidney fibrosis and dysfunction (141).

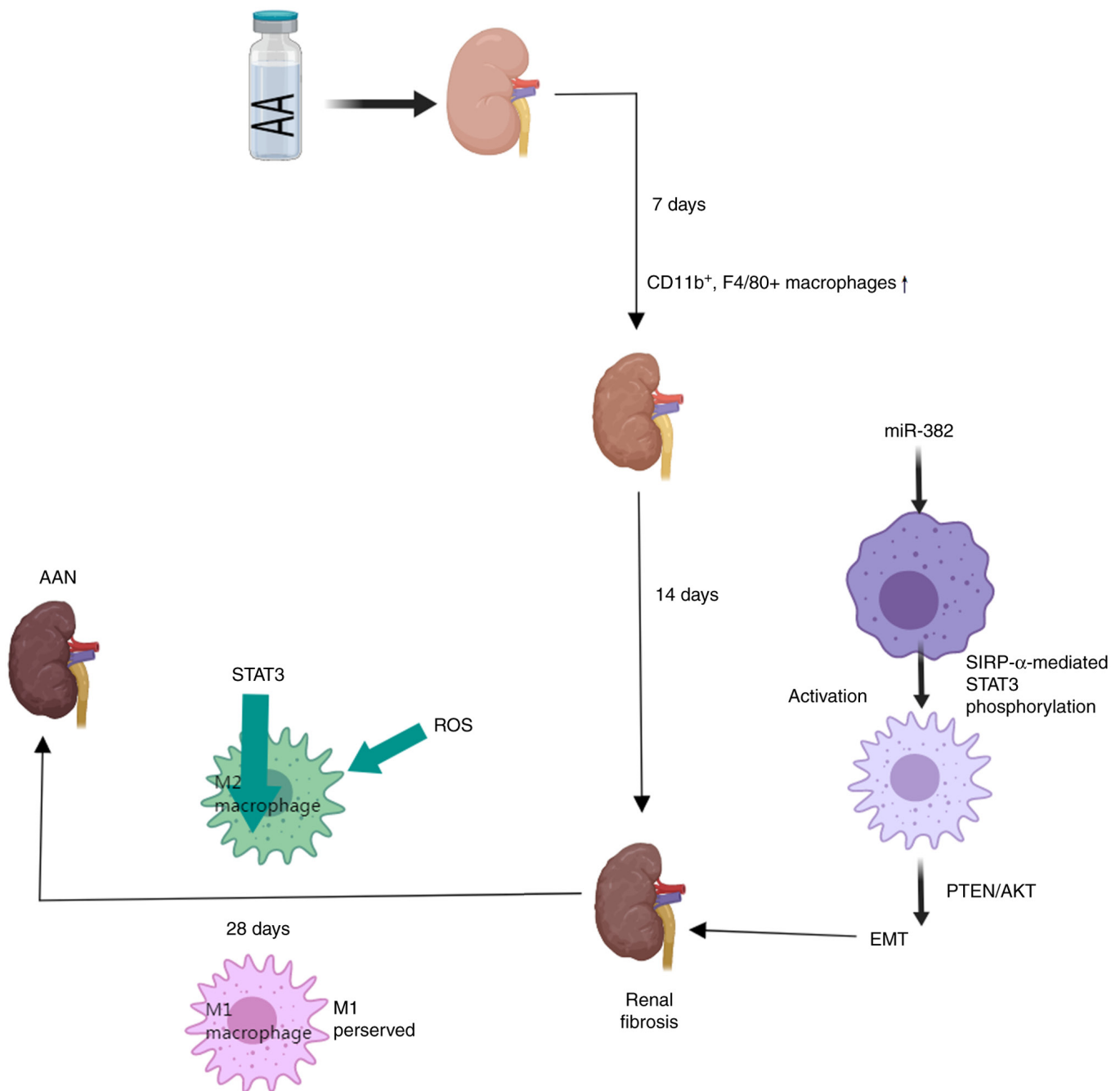


Figure 7. Macrophage polarization in AA Models. AAN is a progressive tubulointerstitial nephritis characterized by tubular atrophy and interstitial fibrosis, marking advanced kidney disease. The activation of STAT3 signaling is associated with AA-induced M2 polarization in macrophages, contributing to the progression of renal fibrosis. ROS production plays a critical role in the activation of M2-differentiated macrophages, rather than M1-like macrophages. The upregulation of miR-382 induced by AA promotes alternative macrophage activation and subsequent interstitial fibrosis through enhanced SIRP- α -mediated STAT3 phosphorylation. AA, aristolochic acid; AAN, AA nephropathy; ROS, reactive oxygen species; miR, microRNA; SIRP- α , signal-regulatory protein- α ; CD, cluster of differentiation; EMT, epithelial mesenchymal transition; AAN, AA nephropathy.

SET domain-containing lysine methyltransferase 7 (also known as SETD7, SET9, SET7/9 or KMT7) is a member of the evolutionarily conserved Su (var) enhancer of zeste and trithorax domain family, initially characterized as a mono-methyl transferase of lysine 4 on histone H3. Evidence indicates the involvement of SETD7 in the pathogenesis of fibrotic disorders. A study (151) demonstrates that PFI-2, a specific and potent SETD7 inhibitor, impairs the transition of M2 macrophages-to-myofibroblasts, reduces the accumulation, of bone marrow-derived myofibroblasts, dampens the inflammatory

response and mitigates the development of renal fibrosis. In this study, SETD7 inhibition was shown to significantly decrease the number of NF- κ B p65⁺ cells in FA-treated kidneys. These findings suggest that SETD7 contributes to the inflammation response in FA nephropathy through the modulation of NF- κ B signaling (151) (Fig. 6). In summary, renal fibrosis represents a crucial pathological aspect of renal diseases. While macrophages play a pivotal role in kidney injury and repair, the functional behaviors of M1 and M2 macrophage cells differ within the context of renal fibrosis induced by FA.

Aristolochic acid (AA)-induced renal fibrosis. In recent years, increased attention has been directed towards the renal toxicity of Chinese herbs. AA is commonly found in various types of Chinese medicinal materials and can also be present in foods contaminated by the environment, leading to kidney injury. The hallmark of the AA-induced renal fibrosis model is the infiltration of activated monocytes/macrophages, which is also a marker of CKD development in humans (152). AA nephropathy (AAN) is characterized by tubular atrophy and interstitial fibrosis, reflecting advanced kidney disease. It is well established that sustained or recurrent episodes of AKI contribute to the progression of CKD. Indeed, in AA-induced renal fibrosis models, an early phase of acute tubular necrosis is rapidly followed by extensive interstitial recruitment of activated monocytes/macrophages and cytotoxic T lymphocytes, leading to a transient AKI episode. Subsequently, a later chronic phase is observed with progressive tubular atrophy resulting from dedifferentiation and necrosis of tubular epithelial cells. The presence of vimentin and α -SMA positive cells expressing TGF- β in interstitial regions indicates an increase in resident fibroblasts and their transformation into myofibroblasts, culminating in collagen deposition and CKD (153).

During AAN, there is a significant increase in CD11b/F4/80+ expression, with the expression of both CD86+ and CD206+ significantly increasing at days 7, 14 and 28 following AA injection. The immunohistochemistry results for anti-F4/80, anti-CD86 and anti-CD206 in kidney tissues are consistent with the aforementioned findings, indicating the accumulation of M1 and M2 macrophages in AAN. Multiple transcription factors are involved in mediating macrophage polarization, including STATs, peroxisome proliferator-activated receptor (PPAR), Krüppel-like factors (KLFs) and C/EBP β (154). Some findings demonstrate that 14 days following the addition of STA-21 (a STAT3 inhibitor), the M2 polarization of AA stimulated macrophages is significantly reduced, while the M1 polarization remained unchanged. Thus, STAT3 activation may contribute to AA-induced macrophage M2 polarization as well as the progression of renal fibrosis (155).

Previous studies have validated that acute AA-I exposure can modulate oxidative stress processes by enhancing ROS production *in vitro*, while simultaneously reducing the ability of macrophages to phagocytose apoptotic neutrophils (156,157). This observation is intriguing and suggests that acute AA-I exposure drives a pro-inflammatory macrophage phenotype with diminished phagocytic capabilities compared to alternatively activated macrophages (158,159). The generation of ROS by macrophages holds significance in a number of physiological processes, particularly those associated with the host's innate immunity responses (160,161). However, ROS release induces not only nitric oxide but also superoxide-anions, hydrogen peroxide and hydroxyl radical, among others, which are associated with mitochondrial respiration (162). Zhang *et al* (161) describe the importance of ROS production in activated M2-differentiated macrophages, but not in M1-like macrophages. Although the nephrotoxicity of AA is well understood, the precise mechanism by which AA contributes to CKD remains largely unknown (162). It has been reported that miR-382, a small endogenous non-coding RNA, functions as a tumor inhibitor by regulating cell apoptosis, or EMT (163). Studies showed that the upregulation of miR-382 promotes

EMT in renal tubular epithelial transcription factors such as IRF4, C/EBP- β , KLF4, STAT3 and 6, PPAR γ that have been shown to promote M2 polarization (163,164). Additionally, it is proposed that AA-induced M2 macrophage polarization and subsequent STAT3 phosphorylation may be mediated by the enhancement of Signal-regulatory protein α (SIRP α) targeting miR-382, a key mediator of STAT3 phosphorylation in S727 and Y705 fibrosis (165,166). Thus, renal fibrosis may be triggered by both M1 and M2 macrophages (42). However, the precise molecular mechanism underlying macrophage polarization remains to be elucidated. Research suggests that NF- κ B is a key regulator of inflammation and its resolution by regulating macrophage polarization (166) (Fig. 7). In summary, the significance of macrophage infiltration, activation and polarization is increasingly recognized as a pivotal driver of meta-inflammation.

4. Macrophage polarization-based therapeutic prospects for renal inflammation and fibrosis

Controlling renal inflammation is arguably one of the most effective strategies for targeting renal fibrosis and maintaining renal function. Understanding the pathways of inflammation is a complex endeavor, with its resolution often dependent on the state of macrophage involvement. However, targeting macrophage-mediated renal fibrosis presents a promising avenue for targeted therapeutics, albeit a challenging one. On the one hand, inhibiting the generation of M1 macrophages and curtailing the progression of renal fibrosis is imperative. On the other hand, maintaining an adequate number of M2 macrophages is essential to facilitate tissue repair and immune regulation. The long-standing association between inflammation and macrophages suggests potential avenues for intervention by focusing on ways to shift macrophage polarization from a pro-inflammatory to an anti-inflammatory state. Thus, further exploration of macrophage polarization is paramount to addressing significant gaps in our understanding. The precise mechanisms underlying macrophage polarization across various experimental models of renal fibrosis and the effects of different macrophage phenotypes remain incompletely elucidated. Therefore, additional investigations are warranted.

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Authors' contributions

JZ wrote the original draft and analyzed the data. CH designed, supervised and edited the manuscript. YZ edited and revised the manuscript and completed the design and production of the figures. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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