Macrophage Migration Inhibitory Factor in Renal Inflammation

Subjects: Immunology

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Renal inflammation is an initial pathological process during progressive renal injury regardless of the initial cause. Macrophage migration inhibitory factor (MIF) is a truly proinflammatory stress mediator that is highly expressed in a variety of both inflammatory cells and intrinsic kidney cells. MIF is released from the diseased kidney immediately upon stimulation to trigger renal inflammation by activating macrophages and T cells, and promoting the production of proinflammatory cytokines, chemokines, and stress molecules via signaling pathways involving the CD74/CD44 and chemokine receptors CXCR2, CXCR4, and CXCR7 signaling. In addition, MIF can function as a stress molecule to counter-regulate the immunosuppressive effect of glucocorticoid in renal inflammation. Given the critical position of MIF in the upstream inflammatory cascade, the regulatory role and molecular mechanisms of MIF in kidney diseases will be focused on.

MIF inflammation macrophages

1. Role of MIF in Acute Kidney Injury

As shown in **Figure 1**, MIF plays a role in acute kidney injury (AKI) under various diseased conditions including renal ischemia, toxicity, infection and sepsis, acute graft rejection, post-renal obstruction, immunologically mediated GN, and congenital anomalies of the kidney and urinary tract (CAKUT). AKI is defined by acute tubular necrosis accompanied by a rapid increase in serum creatinine while decreasing urine output. Increasing evidence shows that AKI is a common kidney disease and a significant global health concern [1]. The etiology of AKI has been widely explored from multiple perspectives including infection, sepsis, renal ischemia, toxicity, and hypoxia [2]. Severe renal inflammation and oxidative stress including the infiltration of macrophages, T cells, and neutrophils, and the upregulation of proinflammatory cytokines are the key pathological processes of AKI [1][2][3][4][5]. Among proinflammatory cytokines such as MCP-1, IL-1β, TNFα, and IL-6, MIF has been shown to be a risk factor of AKI. Indeed, severe renal inflammatory responses may stimulate a rapid release of MIF, resulting in high serum and urinary levels of MIF. In addition, impairments of the glomerular filtration rate and urinary output in AKI patients may be other factors contributing to elevated levels of MIF. Thus, urinary and plasma MIF levels are associated with the development of AKI in patients with acute pyelonephritis [6], severe sepsis and septic shock [7], after cardiac surgery or liver transplantation [8].

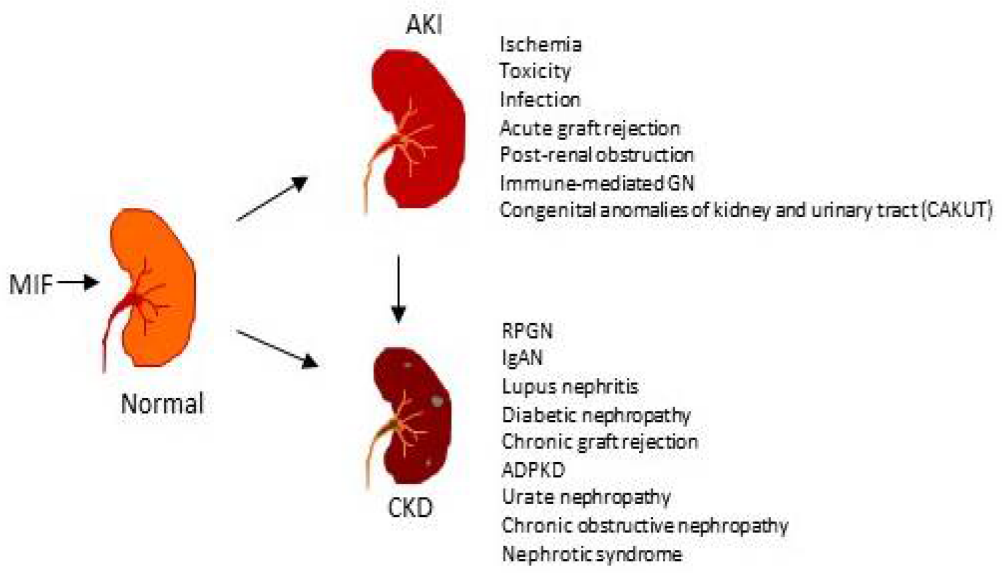

Figure 1. Role of MIF in acute and chronic kidney diseases. Increased exogenous and endogenous MIF can cause AKI and promote AKI-to-CKD, and CKD progression under various disease conditions.

However, it should be pointed out that MIF may play a diverse role in AKI (**Figure 2**). In hypoxia or under severe renal stress conditions, a large amount of MIF is rapidly released and thus triggers severe renal inflammation. Under such conditions, MIF may be pathogenic and play an early role in orchestrating the initial cellular response to tissue injury. Indeed, hypoxia can cause MIF to be rapidly released from pre-formed intracellular pools to trigger the inflammatory response including the expression of MCP-1, TNF-α, IL-1β, IL-6, iNOS, CXCL15(IL-8 in human) and the recruitment and activation of macrophages, neutrophil, and T cells, resulting in severe AKI [9][10]. However, MIF may also play a reparative role in AKI by promoting tubular cell proliferation while inhibiting apoptosis or cell cycle arrest if MIF levels are not sufficiently high to trigger severe renal inflammation. Under this situation, MIF may be protective in AKI as demonstrated in recent studies that mice lacking MIF develop worse AKI by inhibiting tubular epithelial cell proliferation [11][12]. Thus, renal microenvironments may influence the role of MIF.

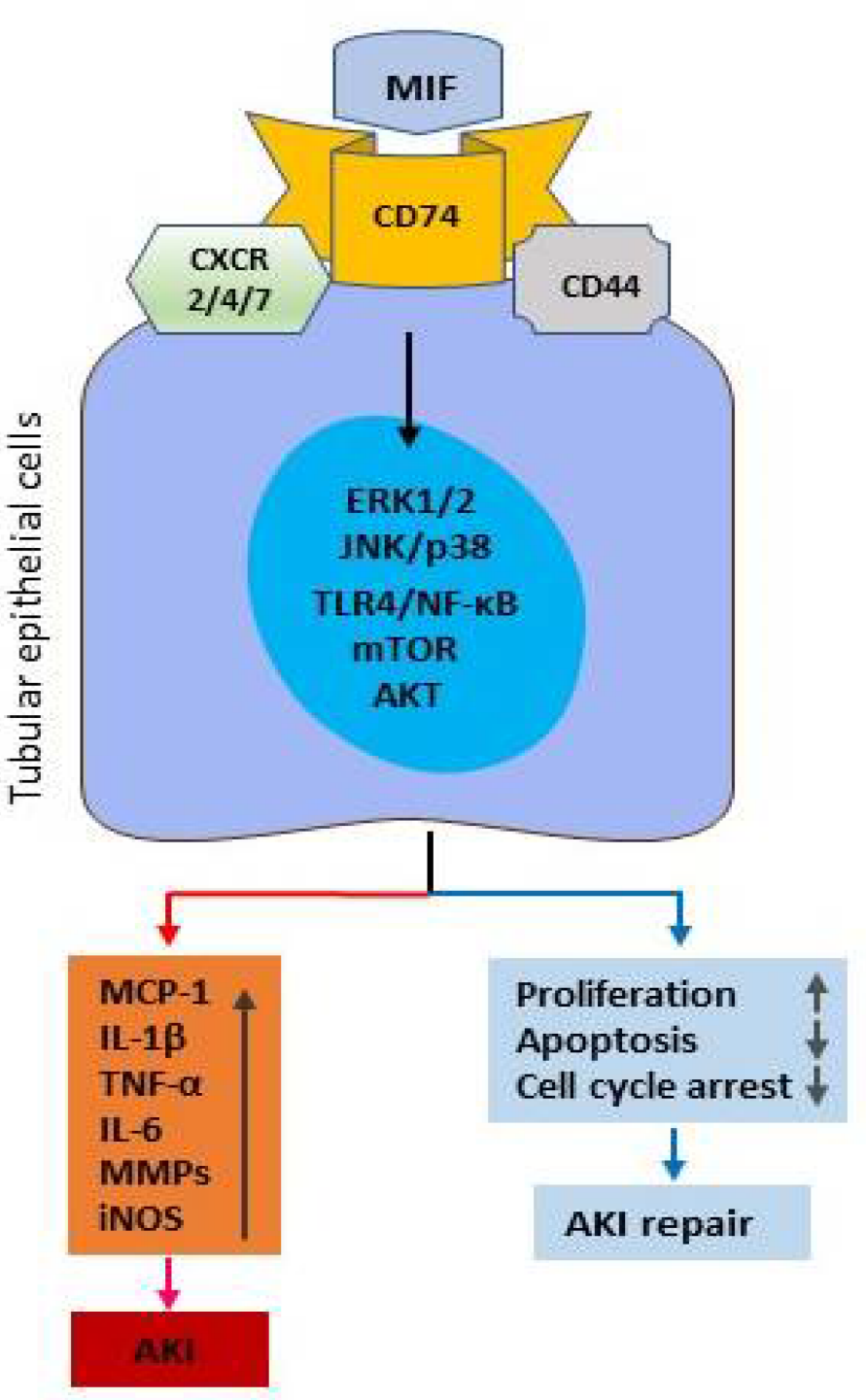

Figure 2. Diverse roles of MIF in AKI. Under certain disease conditions, the overproduction of MIF can promote tubular epithelial cell injury via the proinflammatory mechanisms (the left panel). In contrast, MIF may also activate the downstream pathways to protect tubular epithelial cells from injury by promoting cell proliferation while inhibiting apoptosis and cell cycle arrest (the right panel).

2. Mechanisms of MIF in Kidney Disease

2.1. MIF Receptors and Signal Pathways in Renal Inflammation

MIF is an upstream cytokine in the inflammatory cascade and is released upon stimulation by cellular stress, endotoxin, exotoxin, infection, inflammation, and immune responses. Once released, MIF acts as a proinflammatory cytokine to induce the expression of other inflammatory cytokines/mediators including IL-1, TNF-α, IL-2, IL-6, IL-8, INF-γ, and iNOS to further promote renal inflammation and immune responses by binding to its receptors [13] (**Figure 3**). It is well established that MIF exerts its biological functions in an autocrine and paracrine manner via the CD74, CD44, CXCR2, CXCR4, and CXCR7 receptors [14][15][16][17][18][19]. As illustrated in **Figure 3**, it is also known that the binding of MIF to receptor CD74 to initiate downstream signaling requires the recruitment of CD44 or CXCR receptors [15], including the CD74/CD44 [15][16], CD74/CXCR2 [17], CD74/CXCR4 [18], and CD74/CXCR4/CXCR7 [19]. Although it is not clear whether CD44 is involved in the receptor complexes of CD74 with the CXCRs, the induction of MIF signaling solely via CXCR7 has been reported [20].

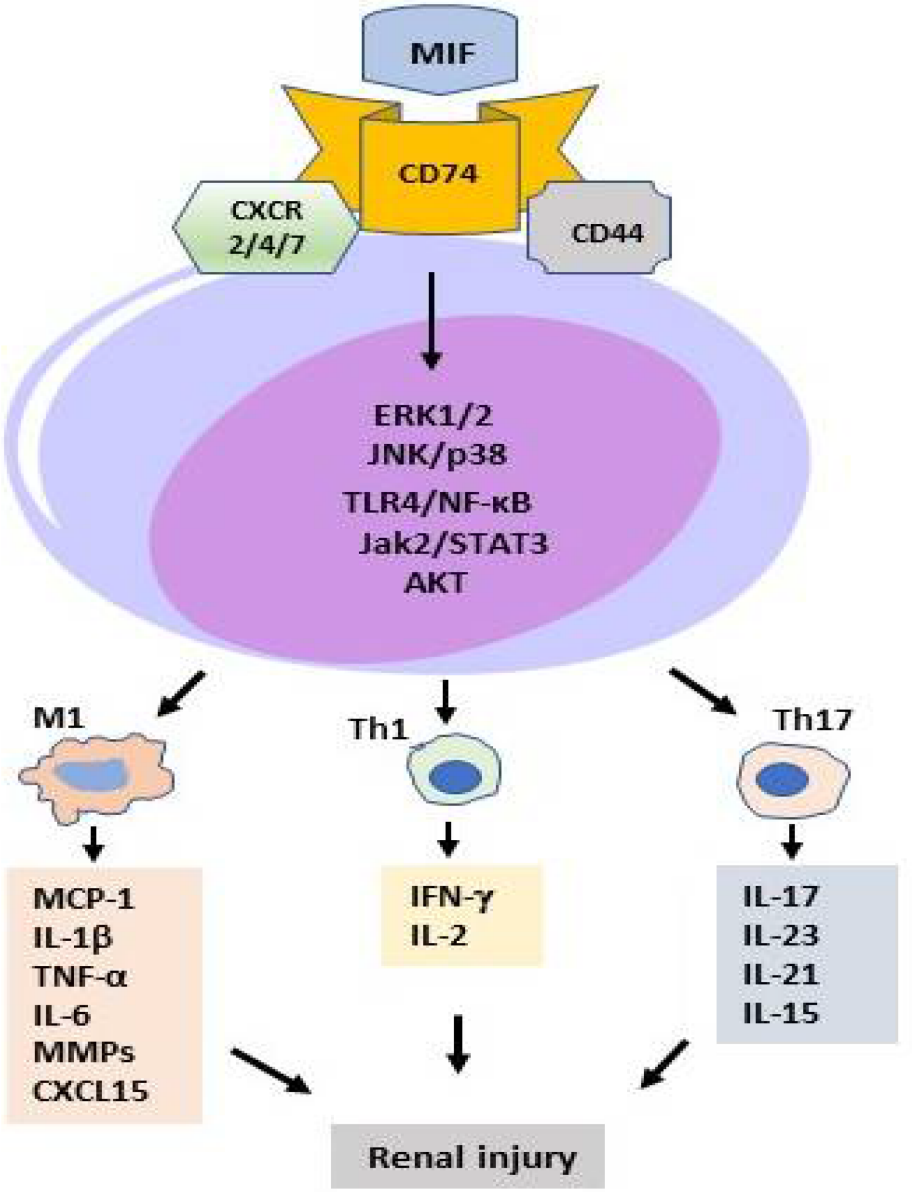

Figure 3. MIF signaling pathways in kidney diseases. After binding to CD74 and CXCRs receptors, MIF can activate the downstream signaling pathways to promote renal inflammation by activating the proinflammatory M1

macrophages and Th1/Th17 immune responses.

In the kidney, CD74 transduces MIF signals in podocytes, tubular cells, and infiltrating inflammatory cells including macrophages and T cells [21]. Once released, MIF binds CD74 to initiate the membrane recruitment of CD44, resulting in the activation of the downstream signal transduction [22][23]. It has been shown that CD74 is markedly upregulated in a diseased kidney with AKI and CKD and MIF mediates acute and chronic injury via CD74/CD44-ERK1/2 or CD74/TLR4-NF-κB-dependent mechanisms [24][25][26][27][28]. In proliferative GN, the upregulation of the podocyte MIF can induce the proliferation of parietal epithelial cells and mesangial cells via the activation of CD74/CD44 signaling [26]. MIF can also induce integrin-β1 and cyclin D1 expression via the ERK pathway to promote cell proliferation and differentiation. These studies indicate a crosstalk between podocytes and parietal epithelial cells via MIF signaling. It was also reported that MIF is the direct target gene of HIF-1α in human primary tubular cells. The tubule-specific knockout of HIF-1α can inhibit MIF upregulation [29]. Furthermore, MIF is also regulated by cAMP signaling to promote cyst growth in ADPKD [29].

2.2. MIF in T Cell-Mediated Kidney Disease

MIF may have a direct or indirect role in recruiting T cells to sites of immune and inflammatory injury as MIF can directly and indirectly activate T cells by inducing the expression of chemokines and adhesion molecules. This is supported by the findings that MIF-producing T cells are exclusively localized to the area of severe tissue injury, including crescentic GN [30][31], IgA nephropathy [31][32], focal glomerular and tubulointerstitial lesions [31], and necrotic vascular inflammation in human renal allograft rejection [33]. MIF may also act by stimulating T cell proliferation and activation to mediate renal injury by promoting the delayed-type hypersensitivity (DTH) and Th1/Th17 immune responses (**Figure 2**). Indeed, MIF is the first T cell cytokine-associated DTH response. Direct evidence for a role of MIF in the DTH response associated with kidney disease comes from the findings that treatment with a neutralizing anti-MIF antibody inhibits skin DTH reaction in the primed mouse model of anti-GBM crescentic GN [34]. Furthermore, MIF can promote Th1/Th2/Th17 inflammatory responses in human primary cell cultures of PBMC from active SLE patients [35]. The absence of MIF results in obesity and inflammation due to the increase in Treg cells in the visceral adipose tissue of MIF-deficient mice, indicating MIF is a new regulator of Treg cells 7 [36]. Evidence of MIF in T cell-mediated kidney disease comes from the observation that T cell-mediated renal injury is prevented in lupus-prone mice targeted for the deletion of MIF [37], whereas treatment with anti-MIF antibody protects against macrophages and T cell-mediated anti-GBM crescentic GN [34].

2.3. MIF in Macrophage-Mediated Kidney Diseases

Macrophages are a rich source of MIF production in the diseased kidney. The researchers find that proinflammatory macrophages produce abundant MIF in both experimental and human kidney disease, including renal allograft rejection [30][31][33][34][38]. In addition, the upregulation of MIF is strongly associated with macrophage accumulation, the severity of tissue injury, and the development of AKI [9][10][24][25][39][40] and crescentic GN [30][31][34][38]. These findings suggest that the local production of MIF by macrophages may, in turn, activate macrophages to produce cytokines (IL-1, TNF-α, IL-2, INF-γ), chemokines (MCP-1), adhesion and oxidative molecules (**Figure 2**).

Evidence to support a critical role of MIF in macrophage-mediated renal injury also comes from the finding that blockade of MIF with a neutralizing MIF antibody is able to prevent or reverse macrophage accumulation and activation in a mouse or rat model of crescentic glomerulonephritis [25][34][38][41].

2.4. MIF as Glucocorticoid Antagonist in Renal Injury

MIF has a unique relationship with glucocorticoids as MIF is also secreted from corticotropic anterior pituitary cells together with ACTH that can stimulate adrenal glucocorticoid secretion. As shown in **Figure 4**, under stress and inflammation conditions, MIF is induced by glucocorticoids but acts as an antagonist of glucocorticoid actions within the immune system to override the immunosuppressive effects of glucocorticoids [42]. MIF overcomes the inhibitory effects of glucocorticoids on TNFα, IL-1β, IL-6, and IL-8 production by LPS-stimulated monocytes in vitro and suppresses the protective effects of steroids against lethal endotoxemia in vivo [42]. Thus, MIF plays a critical role in the host control of inflammation and immunity. MIF-induced renal injury may also be associated with an antagonistic action upon the anti-inflammatory and immunosuppressive effects of glucocorticoids.

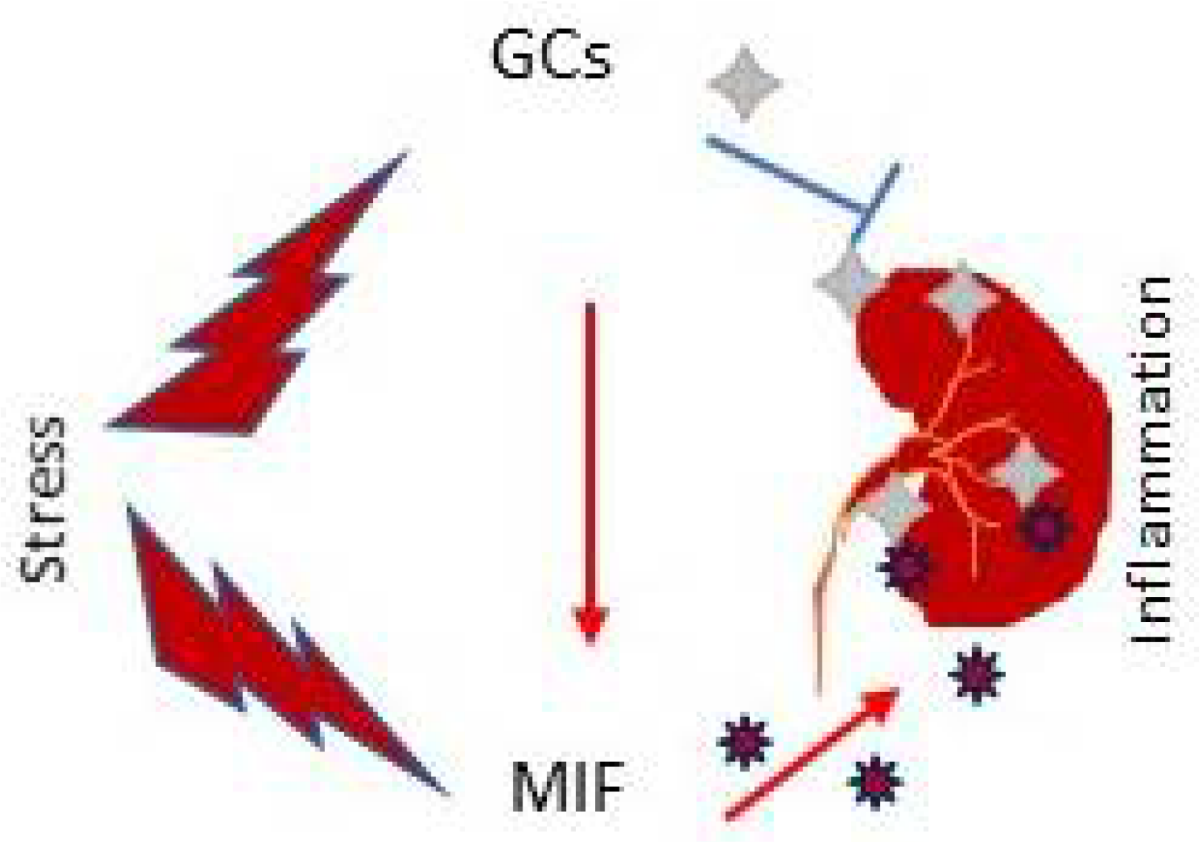

Figure 4. Counter-regulation between MIF and glucocorticoids (GCs) in renal inflammation. Note that MIF and GCs are immediately released in response to the stress stimulation. Once released, GCs can induce MIF to counter-regulate the immunosuppressive actions of GCs, resulting in renal injury.

Glucocorticoids (GCs) are the first-line treatment regimens for most immunologically mediated kidney diseases, including renal transplantation rejection. However, steroid resistance occurs in approximately 20% patients who are at risk pf progression to end-stage kidney disease [43]. Thus, it is possible that targeting MIF may offer better

therapeutic benefits in patients with steroid resistance. By using a comprehensive cytokine analysis in children with idiopathic nephrotic syndrome, MIF plasma levels are increased in patients with steroid resistance and can therefore predict the therapeutic response to GCs [44].

3. MIF as a Therapeutic Target for Kidney Disease

3.1. Antibody-Based Therapy for Kidney Diseases

The development of the neutralizing MIF antibody provided the first evidence of anti-MIF treatment in kidney diseases. In anti-GBM crescentic GN, the administration of the anti-MIF monoclonal antibody immediately after disease induction or at day 7 when the established anti-GBM crescentic GN can attenuate the macrophage and T cell-mediated progressive renal injury, including crescent formation and rapidly renal dysfunctions in a rat model [34][38]. In experimental IgA nephropathy, treatment with an anti-MIF monoclonal antibody is also able to suppress renal injury by inhibiting renal TGF-β1 expression [45]. Interestingly, anti-MIF treatment with a neutralizing antibody can inhibit the skin DTH response without protection against renal allograft rejection [46]. The differential effect of anti-MIF treatment on skin DTH response and acute renal allograft rejection may be associated with the alternative chemokines and cytokines released by a highly active acute renal allograft rejection site to compensate for the inhibitory effect of MIF during acute graft rejection. Thus, treatment with anti-MIF antibody may be disease-type dependent.

3.2. Treatment of Kidney Diseases with MIF Inhibitors

3.2.1. The Methyl Ester of (S, R)-3-(4-Hydroxyphenyl)-4,5-Dihydro-5-Isoxazole Acetic Acid (ISO-1)

ISO-1 is the first MIF inhibitor and has been well studied in several experimental kidney diseases. ISO-1 binds the MIF tautomerase active site and inhibits downstream MIF signaling [47]. The oral administration of ISO-1 into two distinct models of SLE, the NZB/NZW F1 and the MRL/lpr mouse strains, can block the interaction between MIF and CD74, resulting in the inhibition of $CD74^+$ and $CXCR4^+$ leukocyte infiltration, proinflammatory cytokine and chemokine expression, and progressive renal injury in lupus glomerulonephritis [48]. Treatment with ISO-1 in type-2 diabetic db/db mice can also significantly decrease blood glucose, albuminuria, extracellular matrix accumulation, epithelial–mesenchymal transition (EMT), and macrophage infiltration in the diabetic kidney [23]. Furthermore, ISO-1 can also protect against experimental AKI by inhibiting the NLRP3 inflammasome signaling pathway and cell pyroptosis [49][50][51]. These data highlight the feasibility of targeting the MIF-MIF receptor interaction by small-molecule antagonism and support the therapeutic value by targeting MIF in kidney diseases.

3.2.2. Ribosomal Protein S19 (RPS19)

RPS19 is a component of the 40S small ribosomal subunit and binds MIF to block the interaction between MIF and CD74. It has been reported that RPS19 treatment largely prevents the development of anti-GBM crescentic GN by suppressing glomerular crescent formation, glomerular necrosis, and progressive renal dysfunction via

mechanisms associated with inactivating MIF-induced ERK and NF-κB signaling, thereby inhibiting macrophage and T cell infiltration as well as Th1 and Th17 responses [41]. Further study also shows that treatment with RPS19 is capable of attenuating cisplatin-induced AKI by inhibiting MIF/CD74/NF-κB-mediated renal inflammation, which includes suppressing TNF-α and MCP-1 expression and the infiltration of $F4/80^+$ macrophages, neutrophils, and $CD3^+$ T cells in the AKI kidney [41].

3.2.3. Other MIF Inhibitors

Recently, several MIF inhibitors/antagonists have been developed and have been shown to have therapeutic effects on several experimental disease models including diabetes [22][52], bone disease [53][54], and cancer [55]. The blockade of MIF with an MIF antagonist p425 has been shown to significantly decrease urine protein and urine protein/creatinine ratio, serum BUN and creatinine in the streptozotocin-induced diabetic rats [22]. The oral administration of a small-molecule MIF antagonist, CPSI-1306, can also significantly lower blood glucose levels and inhibit proinflammatory cytokines IL-6 and TNF-α expression in a mouse model of streptozotocin-induced diabetes [52]. In addition, other MIF inhibitors including 4-IPP and Chicago sky blue 6B (CSB6B) have also been reported to suppress MIF-induced osteoclastogenesis and osteosarcoma tumorigenesis by targeting NF-κB signaling [53][54][55].

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