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The Role of Macrophage Migration Inhibitory Factor (MIF) in Acute Kidney Injury

ABSTRACT

Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine implicated in acute and chronic disease, including autoimmune disease, atherogenesis, plaque instability, sepsis, glomerulonephritis, acute kidney injury and CKD. Macrophage migration inhibitory factor (MIF) has emerged as a promising therapeutic target in human diseases including immune disorder, cancer, cardiologic diseases, diabetes, and inflammatory diseases. MIF was also reported contributes to leukocyte infiltration, histological damage and renal function impairment in multiple kidney diseases. MIF was considered to be the early prediction of tissue rejection in experimental and clinical transplantation. MIF is increased in many kidney diseases as: acute kidney injury, lipid-induced glomerular injury, rat crescentic glomerulonephritis, anti-GBM diseases, etc. MIF in plasma and urine is significantly elevated in patients with acute kidney injury (AKI) and elevated MIF in serum is associated with renal function and injury, it represents as a biomarker for renal replacement therapy after AKI. This review provides a brief concept of MIF signaling pathway and functional role of MIF in different kidney disease especially AKI.

Keywords: Macrophage Migration Inhibitory Factor; Acute Kidney Injury; MIF Signaling; Renal Inflammation.

EXPRESSION PATTERN OF MIF

Expression of MIF

Macrophage migration inhibitory factor (MIF) was first discovered by Barry Bloom and Boyce Bennett in 1970. They observed a protein from the supernatant of antigen-sensitized lymphocytes could inhibit the migration of macrophages and peritoneal cells [1]. Human MIF cDNA clone and recombinant MIF became available and thus facilitated the analysis of the role of this lymphokine in cell-mediated immunity, immunoregulation, and inflammation over decades [2].

MIF expression has been started at the beginning of life. MIF expression has been detected in multiple tissues and different cell types during organogenesis. MIF mRNA expression was detected in somites, precartilage primordia in ribs and vertebrae, branchial arches, limb buds, neural tissues, all muscle cell types and during organogenesis, lung, liver, kidney, testis, spleen, skin, adrenal gland, intestine, adrenal gland and pancreas [3-6]. All tissues express MIF at baseline

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levels, and it is significantly upregulated under stimulations such as sepsis, stress, or diseased condition. Onset of MIF expression coincides with the specification of tissues, it was observed during myogenesis in all muscle cell types, including cardiac, smooth, and skeletal muscle, during embryonic development [6].

Secretory MIF protein can be detected constitutively in serum and plasma. Historically, MIF was first thought to be produced by activated T-lymphocytes thus considered as a lymphokine, but immunohistochemical analysis of various tissues indicates MIF was also been shown to be secreted from the anterior pituitary gland, monocytes/macrophages, and T and B lymphocytes, NK-cells, basophiles/mast cells and eosinophils activated by various proinflammatory stimuli [7]. MIF was found to be expressed constitutively in anterior pituitary gland, the adrenal cortex, the Leydig-cells of the testis, the epithelial cells of the epididymis and pancreatic β- cells. Other MIF synthesizing cells are vascular smooth muscle, cardiomyocytes and skeletal muscle cells [8], gastric parietal cells [9], keratinocytes and fibroblasts [10], hepatocytes and peripheral and central neurons [4].

Renal MIF is constitutively produced under normal circumstances but significantly upregulated in the kidney-infiltrating T cells, macrophages and various non-immune cells including tubular and glomerular epithelial cells, mesangial cells, endothelial cells, fibroblasts and vascular smooth muscle cells under diseased conditions. Renal MIF is released and exerts its biological activities in many pathological conditions such as septic shock, renal inflammation, immune injury and diabetes.

Regulation of MIF secretion

MIF is normally released at a low rate and in large amounts after stimulation from leukocytes, immune cells and released by injured cells or dead cells. MIF exists in cytoplasm and release directly after stimulation, which is independent to the endoplasmic reticulum and the Golgi, so, no synthesis is necessary before its release [11,12]. Furthermore, MIF expression may increase after conditions of stimulation as stress, sepsis and hypoxia [13]. Thus, in the MIF secretion curve there are two peaks, the first one is formed by MIF releasing from the cytoplasm stores which is the fast and high peak, and then follows the second peak consequent to new MIF synthesis which is the slow and flat peak.

MIF SIGNALING PATHWAY

The receptors of MIF

CD74 is identified as the first and main receptor of MIF [14] and it is an invariant MHC class II cell membrane with high-affinity receptor for bacterial proteins and d-dopachrome tautomerase (d-DT/MIF) [15]. The signals of MIF-CD74 transducing to downstream depends on another receptor CD44, which is a co-receptor of MIF and can interacts with downstream signals as PI3K-Akt, NFκB signaling, etc. CD74 participates in several key processes of the immune system, such as antigen presentation, B-cell differentiation, and inflammatory signaling [16]. MIF and CD74 complex has been shown to regulate peripheral B cell survival. The activation of CD74 also leads to the recruitment of T cells and monocytes, dendritic cell (DC) motility, macrophage inflammation, and thyme selection. CD74 expression was suggested to be as a prognostic factor in many cancers and was suggested to be a predictor of tumor progression [17]. CD74 is a new candidate for immunotherapy of neoplasms, which can be exploited using either a naive anti-CD74 antibody as well as with conjugates including isotopes, drugs, or toxins [18]. CD74 also participates in many human diseases such as inflammatory disease, liver fibrosis, type I diabetes, systemic lupus erythematosus, and Alzheimer disease [19, 20].

Importantly, MIF interacts with extracellular domain of CD74 requires the phosphorylation and the recruitment of CD44 which is a genetically polymorphic molecule with an important role in cell-extracellular matrix interaction to form a MIF/CD74/CD44 complex. It was reported that CD44 play a role in MIF-induced ERK phosphorylation [21]. Study revealed that CD44 deletion partly blocked the inflammatory responses and reduced renal inflammation and injury [22].

Other MIF receptors have been described are the CXC chemokine receptors CXCR2 and CXCR4 which have a relevant role mainly in inflammatory diseases [23]. MIF promotes macrophages and T cells recruit to the inflamed area through binding to CXCR2 and CXCR4. It is also reported that CXCR2 binds to CD74 to form a CD74/CD44/CXCR2 complex which transduce signals downstream.

MIF signaling pathway

MIF has extracellular and intracellular signaling pathways. In extracellular pathway, MIF binds to the extracellular ligands of CD74 which interacts with CD44 to form a complex,

than transduce signals to downstream signaling as MAP kinase to stimulate cell proliferation. In addition, MIF also can indirectly activate NF-κB signaling through a signaling cascade including Src kinase, Akt, Syk, which consequently promotes B lymphocytes proliferation and survival. All this signal activation requires CD74 and CD44 receptors participating and this receptors complex is also required in MIF-mediated anti-apoptotic effects. Moreover, MIF binding to its receptor may also due to the activation of ERK1/2-MAPK, JAB1-CSN5, or PI3K-Akt pathways, the inhibition of p53, and the stimulation of antigenic factors including IL-8 and VEGF. In addition, overexpression of MIF also suppresses anti-tumor activity of the host immune system.

For extracellular pathway: MIF is abundantly existed in the cytoplasm and interacts with other signaling pathways. For example, MIF binds to a coactivator of AP-1 transcription Jab-1 (Jun activation domain-binding protein) [24], inhibits Jab1-mediated JNK activation and then enhances c-Jun phosphorylation. MIF also antagonizes JAB dependent cell cycle regulation, which is shown in **Figure 1** [24].

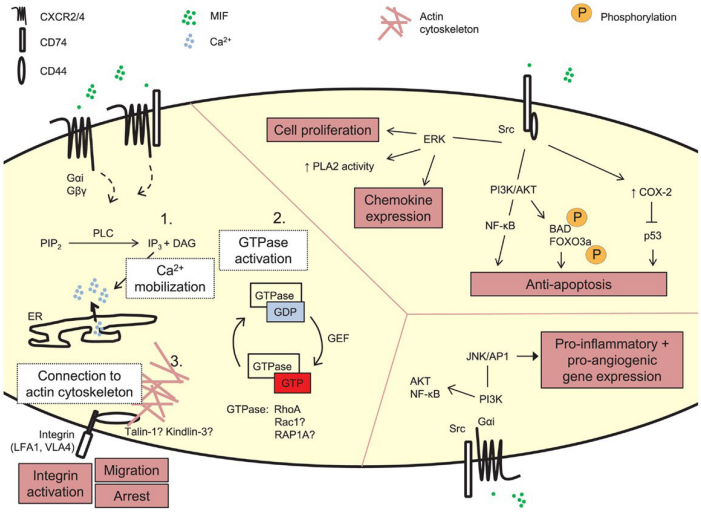

Figure 1: Signaling of MIF. [Sabine Tillmann, Jürgen Bernhagen, Front Immunol., 2013].

MIF IN NON-KIDNEY DISEASES

Macrophage migration inhibitory factor (MIF) has emerged as a promising therapeutic target in human diseases including immune disorder, cancer, cardiologic diseases, diabetes, and inflammatory diseases.

Immune diseases

Increasing evidence shows that MIF is involved in the regulation of T-cell and B-cell developments, dendritic cell (DC) motility, macrophage inflammation, and thymic selection [19]. MIF/CD74 plays an important role in many immune diseases, such as osteoarthritis and rheumatoid arthritis [25], multiple sclerosis [26], Ankylosing spondylitis [27], ANCA-associated vasculitis [28], systemic lupus erythematosus [29]. MIF-deficient MRL/lpr mice have significantly longer survival time and fewer renal and skin injury, where MCP-1 and renal macrophage infiltration were significantly reduced [30]. MIF deletion can protect against disease development of the collagen- and the adjuvant-induced arthritis models [31]. MIF recruits neutrophils via increasing ANCA antigen translocation. The recruited neutrophils can be induced by ANCA further, resulting in respiratory burst and degranulation [28]. MIF is an important element of the inflammatory cascade in rheumatoid arthritis development. Several studies have been demonstrated that the levels of MIF were increased in synovial and serum inRA patients [32,33]. The severity of histological arthritis and cartilage damage, as well as reduced proliferation of synoviocytes was ameliorated in mice lacking MIF [34]. It is also found that MIF promotes leukocyte recruitment in the joint under high endotoxin or TNF condition [35].

Cancers

MIF is recently found to play a prominent role in the cancer progression. Experimental and clinical studies reported that high levels of MIF were observed in a number of human cancers such as Non-small cell lung cancer [36], acute myeloid leukemia [37], breast cancer [38], head and neck squamous cell carcinoma [39], colorectal cancer [40], bladder cancer [41], etc. MIF stimulates the releasing of angiogenic factors that lead to tumor growth and aggressiveness. MIF also triggers the production of cytokines and chemokines in the tumor microenvironments, which suppresses immune surveillance and immune response against tumors, angiogenesis, and carcinogenesis thereby leading to pathological condition e.g. chronic inflammation and immunomodulation [42]. Wu S indicated that MIF promoter polymorphisms (-794CATT) were correlated with the early-stage of cervical cancer [43]. Abdul-Aziz found that MIF was highly expressed in the primary AML [37]. In addition, MIF can increase the myeloid suppressor cells recruitment and is correlated with bladder cancer via CXCL2/MIF-CXCR2 signaling [41]. Bozzi F revealed that MIF/CD74 axis can be taken as a new therapeutic target in colon cancers [44].

Cardiologic diseases

MIF is markedly upregulated in vulnerable atheromatous plaques suggests that MIF may be important in the destabilization of human atherosclerotic plaques [45,46]. Upregulation of myocardial MIF was observed and may contribute to macrophage accumulation in the infarcted area and it may play a pro-inflammatory role in the myocyte damage in AMI [47]. Karin A.L. Mueller described that the level of MIF expression is linked to the degree of myocardial fibrosis with progressive chronic HF in patients. MIF predicted all-cause mortality and the combined study endpoint [48]. In mice myocyte infarction models, the amelioration of cardiac remodeling and incidence of post-MI cardiac rupture (27% vs. 53%) was much lower in MIF KO mice than MIF WT mice [49].

Diabetes

Recently, the term "meta-inflammation" was used to describe the low-grade systemic inflammation status in diabetes and obesity [50]. Increasing evidence suggests that MIF is involved in meta-inflammatory processes. Many studies described genetic polymorphisms of MIF were associated with increased risk of GDM and insulin resistance in diabetic patients, such as genetic polymorphism of rs755622, rs1007888 in MIF, MIF-173GC polymorphism and MIF gene promoter polymorphisms [51-54]. In an animal model of human type 1 diabetes mellitus, MIF was revealed that it plays a critical role in the immune-mediated beta-cell destruction [55]. Other study also indicated MIF influences the molecules expression of Mφ and DC activation in T1DM, the expression of MHC-II, costimulatory molecules CD86, CD80, and CD40, TLR-2, and TLR-4 were lower observed in MIF KO mice than MIF WT mice in induced T1DM model [56]. New MIF inhibitors were revealed could reduce inflammation-caused beta cell death [57]. For example, MIF inhibitor ISO-1 was investigated significantly decreased macrophage activation in db/db mice, accompanied with renal function attenuated and the production of inflammatory cytokines reduced [58]. A significant increase of serum level of MIF was found in patients with T1DM which indicated that MIF could be a therapeutic target for diabetes [59].

Inflammatory diseases

MIF is a pleiotropic cytokine which has chemokine-like functions and plays an essential role in both innate and acquired immunity. Dysregulated MIF expression was seen in various inflammatory conditions [60]. The baseline MIF level and inducible MIF expression in the brain reveals the importance role of MIF in inflammatiory response in neuroendocrine system [4]. MIF also plays a role in cell-mediated hepatic injury in chronic hepatitis B infection [61]. In addition, H. pylori infection is associated with an increasing of MIF expression in gastric epithelial and inflammatory cells [62]. High expression level of MIF alleles is a genetic marker of morbidity and mortality of pneumococcal meningitis [63]. MIF plays a crucial pathological role sustaining the alveolar inflammatory response in ARDS and that anti-MIF and early glucocorticoid therapy may represent a novel therapeutic approach in inflammatory diseases [64,65].

MIF IN KIDNEY DISEASES

It was reported MIF contributes to leukocyte infiltration, histological damage and renal function impairment in multiple kidney diseases.

MIF is constitutively expressed in normal kidney in macrophages, T and B lymphocytes and various non-immune cells including tubular and glomerular epithelial cells, mesangial cells, endothelial cells, fibroblasts and vascular smooth muscle cells [66,67]. MIF was considered to be the early prediction of tissue rejection in experimental and clinical transplantation [68]. MIF is increased in many kidney diseases as: acute kidney injury, lipid-induced glomerular injury [69], rat crescentic glomerulonephritis [66], anti-GBM diseases [70], ANCN-vasculitis, experimental murine MRL/lpr lupus nephritis [71], and unilateral ureteral obstruction (UUO) obstructive nephropathy [72], acute renal allograft rejection [73], acute urate nephropathy [74], aristolochic acid nephropathy [75] and IgA nephropathy [76].

In human kidney diseases, dramatic increase in MIF expression is detected in both glomerular and tubular in proliferative glomerulosclerosis, including lupus nephritis, focal segmental glomerulosclerosis (FGS), crescentic glomerulosclerosis, mesangial-capillary proliferative glomerulosclerosis and allograft rejection [67,77]. Furthermore, infiltrating macrophages and T cells also express MIF, Matsumoto, K. described that peripheral blood T cells isolated from patients with IgAN produced more MIF than T cells from healthy controls or patients treated with corticosteroids [78]. Furthermore, urine MIF level in proliferative glomerulonephritis was increased and correlated with the severity of renal injury [79]. Anti-

MIF neutralizing antibody treatment or MIF deficiency may protect mice from kidney diseases. Blocking MIF activity with anti-neutralizing antibody can partially reverse mice crescentic glomerulonephritis, suggesting that MIF would enhance the cellular immune response [80]. Blocking MIF using a neutralizing antibody [80] or a MIF inhibitor RPS19 [70] can attenuate renal injury by reducing cytokine production, leukocyte infiltrates and 24-hour proteinuria in anti-GBM glomerulonephritis. In another research of a mouse model of IgAN, anti-MIF treatment can ameliorate kidney injury and reduce renal TGF-β1 expression [81].

ACUTE KIDNEY INJURY

Pathophysiology of Acute Kidney Injury

Acute kidney injury (AKI) is one of the causes leading to chronic kidney diseases (CKD) and is related with high mortality rates. The main causes of AKI including prolonged renal ischemia, nephrotoxins, glomerular diseases, obstructed ultrafiltration. The characteristic of AKI is rapidly declined in GFR. Inflammation is an important additional phenomenon of AKI exuberate kidney injury. Renal injury usually affects the highly metabolic active nephron segments in the renal outer medulla, which more likely to suffer kidney injury as reversible conditions of hypoxia to intrinsic renal failure. The essence of the recovery is the injured tubular epithelial cells can restore to normal function and promote regeneration. Recent researchers suggest that AKI has a potential tendency to CKD. Thus, early diagnosis of AKI is essential for treating patients with AKI, and potential biomarkers of AKI may be a promising therapeutic target in the future.

Inflammation and acute kidney injury

Inflammation is the main characteristic of AKI. Inflammation is a significant component of renal I/R injury, playing a considerable role in its pathophysiology. Endothelial injury, generation of inflammatory mediators, leukocyte infiltration largely contributes to the pathogenesis of AKI.

Injury of the kidney contributes to inflammatory response, results in endothelial activation and injury, enhances leukocyte entrapment, endothelial cell-leukocyte adhesion and an accommodation in microvascular blood flow as shown in **Figure 2** [82,83].

The outer medulla is impacted in a greater extent than the cortex during leukocyte-endothelial, which is indicated by the marked vascular overcrowding seen in the outer medulla. Leukocyte subgroups such as neutrophils and T lymphocytes are all contributed to I/R injury [84-86]. Neutrophils from patients with sepsis-induced AKI showed abolished ex-vivo slow rolling, compared with neutrophils from healthy volunteers and patients with sepsis but no AKI. Blocking neutrophil infiltration protects the kidney against ischemic renal injury, even when the antibody was administered after ischemic happened [87]. CD4/CD8 Knockout mice are protected against I/R injury, with a reduction of neutrophils infiltration and T cells adhesion to the renal tubular epithelial cells, suggesting a pathophysiological role for neutrophils and T lymphocytes in AKI [88]. Macrophages infiltrate the injured kidney within 1 hour of ischemia reperfusion and this activity is mediated by fractalkine (CXCL1), both ischemia- and cisplatin-induced AKI triggers fractalkine expression in peritubular capillary endothelial cells. Using anti-CX3C receptor-1 antibody can effectively attenuate the severity of AKI in mice, macrophages lacking CCR do not infiltrate injured kidneys and the resultant injury is less severe[89]; while transferring activated RAW 264.7 macrophages exacerbates kidney injury [89,90].

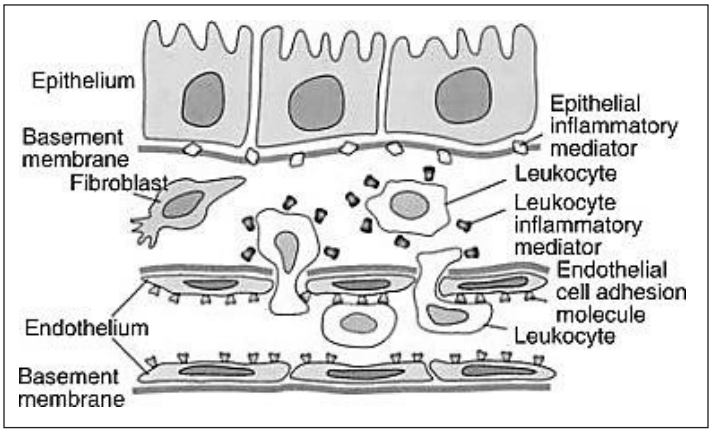

Figure 2: Schematic illustration of the inflammatory mediators produced by tubular epithelial cells and activated leukocytes in renal ischemia/reperfusion (I/R) injury [84] (Joseph V. Bonventre & Anna Zuk, Kidney Int., 2004).

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In addition to the accumulation of leukocytes and endothelial cells injury to the inflammatory response in AKI, the injured tubular epithelial cells and activated leukocytes also generate mediators that exacerbate inflammation including TNF-α, IL-1, IL-6, IL-8, TGF-β, MCP-1, ENA-78, RANTES, and fractalkines [91]; while leukocytes may produce IL-1, IL8, MCP-1, reactive oxygen species and eicosanoids. Both experimental and clinical data have been shown that AKI exerts its regulatory effects on innate immunity via modulating the cytokine homeostasis [92]. In mice model of AKI, the surgery leads to a profound release of proinflammatory cytokines (IL-6 or TNF-α), and remain increased for several days. While sham surgery does not lead to such a prolonged cytokine release [93]. Study indicated TLR4 may also very important at the beginning of transplant. Less MCP-1 and TNFα were detected in the donor kidneys in TLR4 deletion mice but with more heme-oxygenase 1 (HO-1) expression [94]. The decline in renal function during AKI is likely to play a major role in cytokine clearance in a rat model of rhabdomyolysis-induced AKI [95]. This decline in turn led to a sustained increase in plasma cytokine concentrations. Another mechanism cytokine levels are increased in AKI may be augmented production of inflammatory mediators by renal tubular cells in response to injury or cytokines [96,97]. Specific cytokine intervention may offer a new therapeutic hope.

Although significant progress has been made in defining the major components of MIF-mediated AKI, the complex cross talk between endothelial cells, inflammatory cells, and the injured epithelium with each generating and responding to cytokines and chemokines is not well understood.

MIF ASSOCIATED RENAL INFLAMMATION IN AKI

Elevated urinary MIF has previously been observed in AKI during kidney infection in patients, and accompanied with the severity of renal injury in acute pyelonephritis, Brown FG indicated that urine MIF concentration is correlated with the degree of renal dysfunction, histologic damage, and leukocytic infiltration in human glomerulonephritis and has also been suggested as a potential biomarker for acute kidney damage [98,99]. Similar findings have been exhibited in kidney transplantation, urinary MIF was increased on day 1 posttransplantation and changed parallel with the serum creatinine, urine MIF increased even before biopsy proven acute renal rejection [79]. “Severe AKI” had higher levels of plasma IL-10, MIF and IL-6 compared to “no AKI” and “mild AKI” in septic patients admitted to the ICU [100]. In animal models and in vitro studies, MIF induced leukocytes accumulation as well as tissue infiltration of leukocytes thus induces multi-organ damage affecting both lungs and kidneys, treatment with anti-MIF antibody attenuated pulmonary pathology in mice with LPS-induced acute lung injury or anti-GBM glomerulonephritis via reducing the upregulation of IL-1β, ICAM-1 and VCAM-1 [101-103]. Recently study reported that plasma MIF level in was elevated in AKI patients after orthotropic liver transplantation patients and was more valuable in identifying the prognosis of AKI and predicting the requirements of renal replacement therapy after operation [104]. MIF and its receptor CD74 may be useful targets to reduce neutrophilic inflammation in acute lung injury [101]. In heart, the upregulation of MIF levels contributes to AMPK activation thus protects mice from heart infarction [105]. The mechanism of MIF in the progression of AKI is needed to be further elucidated.

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