Immunomodulatory Effects of Mesenchymal Stem Cells on Drug-Induced Acute Kidney Injury

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Drug-induced nephrotoxicity is an important and increasing cause of acute kidney injury (AKI), which accounts for approximately 20% of hospitalized patients. Previous reviews studies on immunity and AKI focused mainly on ischemia-reperfusion (IR), whereas no systematic review addressing drug-induced AKI and its related immune mechanisms is available. Recent studies have provided a deeper understanding on the mechanisms of drug-induced AKI, among which acute tubular interstitial injury induced by the breakdown of innate immunity was reported to play an important role. Emerging research on mesenchymal stem cell (MSC) therapy has revealed its potential as treatment for drug-induced AKI. MSCs can inhibit kidney damage by regulating the innate immune balance, promoting kidney repair, and preventing kidney fibrosis. However, it is important to note that there are various sources of MSCs, which impacts on the immunomodulatory ability of the cells. This review aims to address the immune pathogenesis of drug-induced AKI versus that of IR-induced AKI, and to explore the immunomodulatory effects and therapeutic potential of MSCs for drug-induced AKI.

Keywords: acute kidney injury, mesenchymal stem cell, immunomodulation, cell therapy, kidney repair, drug-induced AKI, ischemia-reperfusion

INTRODUCTION

In the past decade, pharmaceutical companies have developed many life-saving drugs for patients with cancer. Unfortunately, some of these drugs are associated with nephrotoxicity, which remains an important and more frequent cause of acute kidney injury (AKI). Currently, AKI represents a serious global public health challenge, with significant adverse economic and medical burden, that affects approximately 13.3 million people annually (1, 2). Drug-induced AKI is a particularly important category, accounting for 19–26% of AKI cases (2). The use of nephrotoxic drugs is the main cause of severe AKI in critically ill patients. Moreover, drug-induced nephrotoxicity is one of the main factors leading to unsuccessful drug development, leading to loss of money and time in the pharmaceutical industry (3). Notably, approximately 19% of phase 3 clinical trial failures are caused by nephrotoxicity (3).

Recent studies have provided a deeper understanding of the mechanisms underlying drug-induced AKI. In particular, oxidative stress was shown to activate inflammatory responses, by promoting the release of pro-inflammatory cytokines and the accumulation of inflammatory cells in tissues, which supports the progression of AKI (4). Mesenchymal stem cell (MSC) therapy has been considered to hold great potential for the treatment of drug-induced AKI given its powerful immune regulatory effects (5). Previous studies on the immune pathogenesis of AKI and MSC therapy mostly focused on ischemia-reperfusion (IR), but drug-induced AKI is also important and needs more attention. The immune pathogenesis of IR and drug-induced AKI were reported to be different, which may also impact on the efficiency of MSC treatment on drug-induced AKI. Therefore, the differences between these two types of AKI could provide a good reference for scientists to explore MSC-based treatment strategies for drug-induced AKI in the future. In addition, it is very important to notice that MSCs can be derived from various sources and their immunomodulatory ability may differ based on their origin. When using MSCs for clinical treatment of patients, it should be considered the difficulty of obtaining these cells, as well as the number of cells and ethical limitations. Therefore, understanding the immunomodulatory ability, proliferative potential, and clinical application characteristics of MSCs from different sources can aid to choose the most appropriate MSC population for clinical use in AKI treatment.

In this review, we provide an in-depth, comprehensive summary of the immune pathogenesis of drug-induced AKI and subsequent molecular mechanisms, including the different types of immune cells, cytokines, and related signaling pathways. The immunomodulatory effects of MSCs for the treatment of drug-induced AKI were also explored based on the latest research progress. In particular, we compared the different immune pathogenesis of drug-induced and IR-induced AKI, as well as the different immune regulatory abilities of MSCs from different sources.

DRUG-INDUCED AKI AND COMMON NEPHROTOXIC DRUGS: THE CISPLATIN EXAMPLE

Several recent, large-scale epidemiological studies have shown that nephrotoxic drugs cause severe acute renal failure in many critically ill patients (2), for whom the use of potentially nephrotoxic drugs is, in most cases, unavoidable (6). Drug-induced AKI usually presents as one of two types: acute tubular necrosis, which is directly related to nephrotoxicity to the renal tubular epithelial cells, or immune-mediated acute interstitial nephritis, which develops from drugs that cause allergic reactions. Approximately 60% of patients with hospital-acquired AKI experience nephrotoxic induced by medications (7). Among the various cellular mechanisms of drug-induced AKI, the most important is the accumulation of inflammatory cells in the tissue, which in turn activates the

inflammatory response and oxidative stress that triggers the release of pro-inflammatory factors. Nephrotoxic injuries often occur in the proximal renal tubules due to the administration of cisplatin, aminoglycosides (gentamycin, kanamycin, streptomycin, or tobramycin), amphotericin B, antiviral agents (adefovir, cidofovir, or tenofovir), radiocontrast, bisphosphonate, among other drugs (4).

Cisplatin is a chemotherapy drug, and is the most classic and commonly used model for basic research on drug-induced AKI, with a reported frequency of cisplatin-induced AKI ranging from 20% to 30% due to dose-limiting side effects in the treatment of various solid cancers, including testicular, ovarian, cervical, breast, lung, head and neck, bladder, and gastric cancer (8). Although there are other less common cisplatin-induced toxicities (such as ototoxicity, gastrotoxicity, and myelosuppression), nephrotoxicity has a major impact on the patient health and should be the first side effect to be monitored and evaluated in patients undergoing cancer chemotherapy. Notably, the accumulation of toxic intermediates in the kidney limits the use of cisplatin, which leads to incomplete chemotherapy. Therefore, the mechanism reviewed hereafter is mainly based on basic research conducted with the cisplatin-induced AKI model.

The typical histological features of drug-induced AKI are severe tubule damage comprising lumen dilation, significant cytoplasmic simplification, increased cytoplasmic eosinophilia, and disappearance of brush borders and of the tubule epithelium. First, several events, such as loss of polarity and cytoskeletal integrity, and cell necrosis and apoptosis, occur in the proximal tubular epithelial cells of the kidney over time (9, 10). Subsequently, necrosis induces inflammation, and damage-associated molecular patterns (DAMPs) and other pro-inflammatory molecules are released, resulting in the activation of the innate immune system via membrane surface receptors. Inflammatory cells, such as white blood cells, are recruited into the peritubular interstitium. Furthermore, inflammation accelerates the damage to the renal tubular tissues and causes necroptosis and the release of tumor necrosis factor alpha (TNF-α) and other inflammatory factors that continue to drive cell necrosis. This leads to tubular necrosis and renal insufficiency, forming an inflammation-necrosis amplification loop (11, 12). Another mechanism of drug-induced AKI is oxidative stress. Drug nephrotoxicity directly acts on the proximal renal tubules and causes cell damage, such as mitochondrial dysfunction, lysosomal hydrolase inhibition, phospholipid damage, and increased intracellular calcium concentrations, thereby leading to the formation of reactive oxygen species (ROS) (13). The pathogenic mechanisms of ROS have three main aspects: first, nephrotoxic drugs react with cellular antioxidants (such as glutathione) when they are in a highly reactive form (14, 15), thus, depleting or inactivating them, leading to the accumulation of endogenous ROS in cells. ROS activates the intracellular mitogen-activated protein kinases, p53, p21, and other pathways, leading to the death of renal tubular cells. Second, ROS directly or indirectly promotes fibrosis by promoting tissue inflammation. Fibrosis and

inflammation will, in turn, promote positive feedback pathways, further increasing ROS production and stimulating the secretion of inflammatory factors. Third, nephrotoxic drugs affect the normal respiration of mitochondria, making them dysfunctional and increasing the production of ROS (16).

DIFFERENT IMMUNE MECHANISMS OF DRUG-INDUCED AND IR-INDUCED AKI

AKI is mainly triggered by IR injury, which causes high morbidity and mortality in both adults and children (17). IR-induced AKI results from acute hypoxia caused by reduced blood perfusion in the renal tissue, which is prone to occur in the renal tubule region. Reperfusion leads to the production of metabolites, such as nitric oxide and ROS, which can damage the cell membranes and lead to cell apoptosis. However, drug-induced AKI is more common in infants and older people with underlying cardiovascular diseases and renal dysfunction, such as intravascular volume depletion, diabetes, congestive heart failure, chronic kidney disease, and sepsis (18, 19). Drug-induced renal injury, which results from the direct damage to the renal tubular epithelial cells, occurs when the increasing concentration of nephrotoxic drugs in the renal tubule reaches a toxic level. Therefore, the degree of damage is related to the drug dose administrated. Noteworthy, there are several differences in the pathogenesis of IR-induced and drug-induced AKI; however, there are very limited systematic reviews comparing the differences in the pathogenesis between these two models. Understanding the differences in their immune pathogenesis may be helpful for the management of AKI. A summary of these differences is provided in **Table 1**.

T cells play an important role in AKI. In IR-induced AKI, $CD8^+$ cells have no obvious pathogenic effects. However, in the cisplatin-induced AKI model, CD8-deficient mice had significantly less damage than wild-type mice, indicating that $CD8^+$ cells have an important pathogenic role in this model (20). No obvious differences in other subpopulations of T cells were found between the two models. During the inflammatory response to IR injury, the main role of renal dendritic cells (DCs) is to serve as antigen-presenting cells to T cells, release TNF-α, upregulate adhesion molecules, and promote leukocyte extravasation (21, 22). However, renal DCs play a protective role in drug-induced AKI. In one study, infiltration of DCs in damaged tissues resulted in secretion of cytokines such as interleukin (IL)-10 to prevent AKI progression (23). In the IR model, inhibition of neutrophil recruitment can significantly reduce kidney damage, which suggests that neutrophil infiltration is one of the pathogenic mechanisms of renal IR injury (24). In contrast, inhibition of neutrophil infiltration has no effect on cisplatin-induced kidney injury, indicating that neutrophil infiltration is not necessary for cisplatin-induced kidney damage (25). Importantly, macrophages have pro-inflammatory (M1) and anti-inflammatory (M2) cell phenotypes and their roles in the two AKI models are similar (26), with M1 cells being dominant in the damage stage, whereas M2 cells playing an important role in the repair stage. In addition, the relationship between the complement system and AKI has been studied more in the IR injury model than in the drug-induced AKI model. However, the mechanism of action of the complement system in both models is mainly mediated by the activation of the complement component 5a and its receptor (C5a/C5aR)–nuclear factor kappa B (NF-κB) pathway (27).

Cytokines and chemokines are differently expressed in drug-induced and IR-induced AKI, which may be due to the different cellular origins and actions of the molecules. IL-11 is upregulated in IR-induced (but not in cisplatin-induced) AKI (28). In addition, inhibition of IL-18 can significantly reduce IR-induced renal injury but not cisplatin-induced nephrotoxicity (29), which suggests that IL-18 may be an important factor in IR-induced AKI. Moreover, the expression of the C-C motif chemokine ligand (CCL) 5 and IL-1α is significantly increased in cisplatin-induced AKI, but only slightly increased in the IR injury model (28). Furthermore, TNF-α-deficient mice are resistant to cisplatin nephrotoxicity, thereby suggesting that TNF-α plays an important role in the pathogenesis of

TABLE 1 | Comparison of the immune mechanisms between drug-induced and ischemia reperfusion-induced AKI.

Immune system component	Mechanism of IR-induced AKI (e.g., organ grafting)	Mechanism of drug-induced AKI (e.g., cisplatin)
T cells	$CD8^+$ cells have no obvious pathogenic effect in IR injury (20).	Inhibition of $CD8^+$ can significantly improve kidney damage (20).
Dendritic cells	Higher proportion of mature dendritic cells, antigen presentation effect and pro-inflammatory response (21, 22).	Higher proportion of immature dendritic cells, promote kidney repair (23).
Neutrophils	Infiltration at the injury site, but inhibition of neutrophils can significantly reduce kidney damage (24).	Infiltration at the injury site, but inhibition of neutrophils cannot significantly reduce kidney damage (25).
Macrophages	Macrophages have similar actions in drug-induced and IR-induced AKI. M1 cells are the dominant cells in damage stage; M2 cells play a role in tissue repair (26).	
Complement system	The mechanism of action of the complement system in drug-induced and IR-induced AKI involves the activation of C5a/C5aR–NF-κB pathway (27).	
Cytokines/pathway	The levels of IL-11 increase (28).	The levels of IL-11 do not increase (28).
	Inhibition of IL-18 can significantly prevent kidney damage (29).	Inhibition of IL-18 cannot significantly prevent kidney damage (29).
	CCL5 and IL-1α slightly increase (28).	CCL5 and IL-1α significantly increase (28).
	Inhibition of TNF-α cannot significantly reduce kidney damage (28).	Inhibition of TNF-α can significantly reduce kidney damage (28).
	NLRP3 pathway is the key pathogenesis of inflammation (30).	NLRP3 pathway is less important (30).

AKI, acute kidney injury; C5a, complement component 5a; C5aR, complement component 5a receptor; CCL5, C-C motif chemokine ligand 5; IL, interleukin; IR, ischemia-reperfusion; M1, pro-inflammatory macrophages; M2, anti-inflammatory macrophages; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; TNF, tumor necrosis factor.

cisplatin-induced renal injury. Accordingly, TNF-α inhibitors can ameliorate renal dysfunction and reduce the structural damage caused by cisplatin, and inhibition of TNF-α more effectively reduce cisplatin-induced than IR-induced kidney damage (28). In addition, the nucleotide-binding oligomerization domain-like receptors (NLR) family pyrin domain containing 3 (NLRP3) pathway is critical in the pathogenesis of IR-induced AKI, but is less important in cisplatin-induced AKI (30).

DIFFERENT IMMUNOREGULATION CAPABILITY OF MSCS FROM VARIOUS ORIGINS

MSCs are pluripotent stem cells with anti-inflammatory and immune tolerance potential (31), which were first identified in the bone marrow stroma where supported the development and differentiation of hematopoietic stem cells. In recent years, with research advances, MSCs have been increasingly used in clinical practice given their immunosuppressive functions and tissue repair ability (32). Hence, stem cell therapy is another medical revolution that may be considered after drug therapy and surgical treatment. MSCs can easily expand in vitro into high numbers in a short period of time. This is an important prerequisite for MSCs that are widely used in experimental research and clinical practice, including AKI treatment (33). Moreover, MSCs can be cultured from adipose tissue, cord blood, umbilical cord, placenta, and fetal lungs. However, the biological characteristics of the MSCs originating from these various tissues are different, especially concerning their immune regulation capacity (34). The immunological activity of MSCs from different tissues may differ because of the different original activation states of these cells in the source tissues (35–37). The differences in the immunomodulatory ability, proliferation potential, and clinical application characteristics of MSCs from different sources is summarized in **Table 2**.

Current studies have shown that the immunological activity of MSCs originating from different tissues is "strong" or "weak" rather than "present" or "absent" (38). Yoo et al. compared the immune regulatory functions of adipose-derived MSCs (AD-MSCs), umbilical cord blood-derived MSCs, umbilical cord-derived MSCs (UC-MSCs), and bone marrow-derived

MSCs (BM-MSCs) on T lymphocytes (34), and found that all four types of MSCs inhibited the proliferation of activated T cells and the secretion of interferon-γ and TNF-α. Moreover, Bochev et al. found that both BM-MSCs and AD-MSCs could inhibit the secretion of immunoglobulins by activating B lymphocytes (39). However, the inhibitory effects of AD-MSCs on immunoglobulin secretion were stronger than those of BM-MSCs. Some study also reported that AD-MSCs have higher indoleamine 2,3-dioxygenase (IDO) activity and secret more IL-6, IL-10, and transforming growth factor (TGF)-β than BM-MSCs (35, 40). Moreover, Barcia et al. found that compared with BM-MSCs, UC-MSCs have stronger immunomodulatory abilities, can more efficiently inhibit CD3- and CD28-induced lymphocyte proliferation, and can more efficiently induce the production of $CD3^+CD4^+CD25^+Foxp3^+$ regulatory T cells (Tregs) (41).

Nevertheless, some studies have shown that the in vitro expansion capabilities of MSCs from different tissues are not completely the same. Different microenvironments may be the reason for these differences. Li et al. compared the proliferative capacity of BM-MSCs and AD-MSCs, and found that AD-MSCs have stronger proliferation potential (42). However, as the age of the donor increases, the number and proliferation capacity of BM-MSCs and AD-MSCs significantly decreases. MSCs derived from perinatal tissues (such as umbilical cord, placental chorion, and amniotic membrane) have much stronger proliferation potential than BM-MSCs. Comparing MSCs isolated from umbilical cord tissue and bone marrow, more MSCs can be obtained from umbilical cord tissues, and with greater proliferation ability than BM-MSCs (43). After 30 generations, the proliferative capacity of UC-MSCs did not change significantly, whereas BM-MS showed weakened proliferation ability and prolonged doubling time after six passages.

In summary, perinatal MSCs (MSCs derived from the umbilical cord and placenta) generally have higher immunomodulatory capabilities, while BM-MSCs show higher potential to support the regeneration process, such as neuronal differentiation and development (43). These differences between perinatal and bone marrow-derived MSCs may impact on their clinical application. In addition, when MSCs are used in the clinical treatment of diseases, the feasibility of its acquisition, the number of cells, and ethical limitations must be considered. For example, BM-MSCs and AD-MSCs have several limitations. They are generally obtained from adults and the number of

TABLE 2 | Immunomodulatory ability, proliferation potential, and clinical application characteristics of MSCs from different sources.

Source	Immunomodulatory ability[1]	Proliferation potential[1]	Clinical application characteristics
Bone marrow	+	+	The related research started earlier and is more thorough. The number of cells that can be extracted is relatively small. The passage ability that can maintain the characteristics is weak.
Umbilical cord	+++	+++	The number of extractable cells is obviously more than that of bone marrow. Strong ability of passage. No ethical limit.
Placenta	+++	+++	The number of extractable cells is more than that of umbilical cord and bone marrow. No ethical limit.
Adipose tissue	++	++	Easy to get relatively large number of cells from rich resource of adipose tissue. Whether the cells can adapt to the environment in vivo remains to be further studied.

[1]Higher number of + represents a stronger degree.

cells available is limited. Moreover, there are restrictions regarding the age of the donor. However, MSCs in the perinatal period have stronger expansion capacity and have no ethical restrictions. After expansion, the basic properties and morphology of MSCs have no obvious changes, so that a large number of MSCs can be obtained from the same sample to meet the needs of the clinical cell therapy (43). Therefore, compared with adult-derived stem cells that proliferate slowly, perinatal MSCs have unique advantages. From this perspective, MSCs derived from umbilical cord and placenta are an ideal choice.

IMMUNOMODULATORY EFFECTS OF MSCS ON DRUG-INDUCED AKI

The strong ability of MSCs to differentiate is one of the main mechanisms contributing for tissue damage repair. Although the initial focus on MSCs was on their regenerative ability to differentiate into various tissue cell types (33), more attention is currently addressed onto their ability to regulate immune responses (44). *In vivo* and *in vitro* studies have shown that MSCs can directly inhibit the proliferation, differentiation, and effector mechanisms of T cells by preventing the externalization and maturation of DCs. In addition to T cells and DCs, the target cells of MSCs include many other types of immune cells, including natural killer cells, B cells, neutrophils, and macrophages (45). MSCs regulate the function of these cells, including the secretion of cytokines and their subsequent cytotoxic effects, eventually exerting anti-inflammatory effects and/or inducing an immune tolerance state. To date, the immune regulation mechanisms of MSCs remain poorly understood, but it is generally believed that MSCs have an immunosuppressive function mainly through cell-to-cell contact with a variety of immune cells and secretion of soluble factors, such as prostaglandin E2 (PGE2) and IDO, thereby reducing tissue damage caused by inflammation (46). MSCs have low immunogenicity, that is, MSCs do not express major histocompatibility complex class II molecules or costimulatory molecules, and do not cause the activation and proliferation of allogeneic lymphocytes, which provides the possibility for the clinical application of allogeneic MSCs transplantation (47). These cells inhibit the proliferation of activated T lymphocytes and the secretion of interferon-γ, the proliferation of B lymphocytes and the secretion of immunoglobulins, the killing activity of natural killer cells, the differentiation of M1 macrophages, the secretion of pro-inflammatory factors, and the differentiation of monocytes into DCs (48).

There is a very close connection between the immune system and the kidney system (49). Pro-inflammatory DAMPs, pathogen-associated molecular patterns (PAMPs), toll-like receptors (TLRs), oxidative stress, complement system, resident DCs, neutrophils, T lymphocytes, macrophages, and secreted cytokines and chemokines, all participate in the immunopathological mechanism of drug-induced AKI and promote disease progression (20, 28, 50–53). Therefore, imbalance of the immune system has a direct or indirect impact on the progression of kidney disease. If the immunopathological process of AKI continues, this may lead to renal fibrosis and/or chronic kidney disease. The immunomodulatory mechanism of MSCs in AKI treatment is shown in **Figure 1**.

THE IMMUNE MICROENVIRONMENT OF DRUG-INDUCED AKI

T Cells
Approximately 30% of the circulating white blood cells in healthy adults are T cells from the thymus (51). T cells are important immune regulators of drug-induced AKI, as T cell infiltration was observed in damaged renal tissues within 1 h after cisplatin administration, which reached a peak at 12 h and decreased after 24 h (54). Compared with wild-type mice, T cell knockout significantly improved renal function and prolonged survival in cisplatin-induced AKI mice. Furthermore, infiltration of neutrophils and macrophages into the kidney was reduced in T cell knockout mice, suggesting that T cells play a critical role in the recruitment of immune cells to the site of injury. CD4+ T cells are activated and quickly infiltrate the damaged kidneys, mediating further renal tissue damage (54, 55). Depending on the regulation of the immune microenvironment, naïve CD4+ cells can differentiate into helper T cells (Th) or Tregs, and play different roles. Cisplatin nephrotoxicity causes naïve CD4+ T cells to differentiate into Th, resulting in a strong immune response and kidney damage. Tregs are believed to play a protective role against cisplatin-induced AKI. They enter the kidney tissue and directly modulate the response of cells to inhibit the pro-inflammatory signals promoted by cisplatin toxicity, reduce renal macrophage infiltration, as well as the levels of TNF-α and IL-1β, thereby reducing renal dysfunction. CD4+ T cells complete the immune response to cisplatin through the paracrine pathway (secreting TNF-α, IL-17, IL-33, and IL-10), whereas cytotoxic CD8+ T cells induce renal cell injury in a contact-dependent manner (54). Cisplatin can upregulate the expression of Fas receptors on damaged renal tubular epithelial cells, allowing it to interact with Fas ligands on CD8+ T cells infiltrating the kidney, and then trigger the apoptosis of damaged cells (49). MSCs can inhibit the production and activation of Th and CD8+ T cells, and reduce inflammation in cisplatin-induced AKI. Furthermore, MSCs promote the differentiation of naïve CD4+ T cells into Tregs by secreting hepatocyte growth factor, TGF-β, PGE2, and IDO, which in turn secrete IL-10. Moreover, PGE2 and IDO secreted by MSCs can promote the differentiation of macrophages into the anti-inflammatory M2 phenotype (56). Therefore, the anti-inflammatory effects of MSCs can be further improved, and the kidney damage caused by cisplatin can be reduced.

Dendritic Cells
DCs are the most common immune cells that maintain renal homeostasis. Renal DCs are located between the renal tubules and the peritubular capillaries. They act as effector cells and
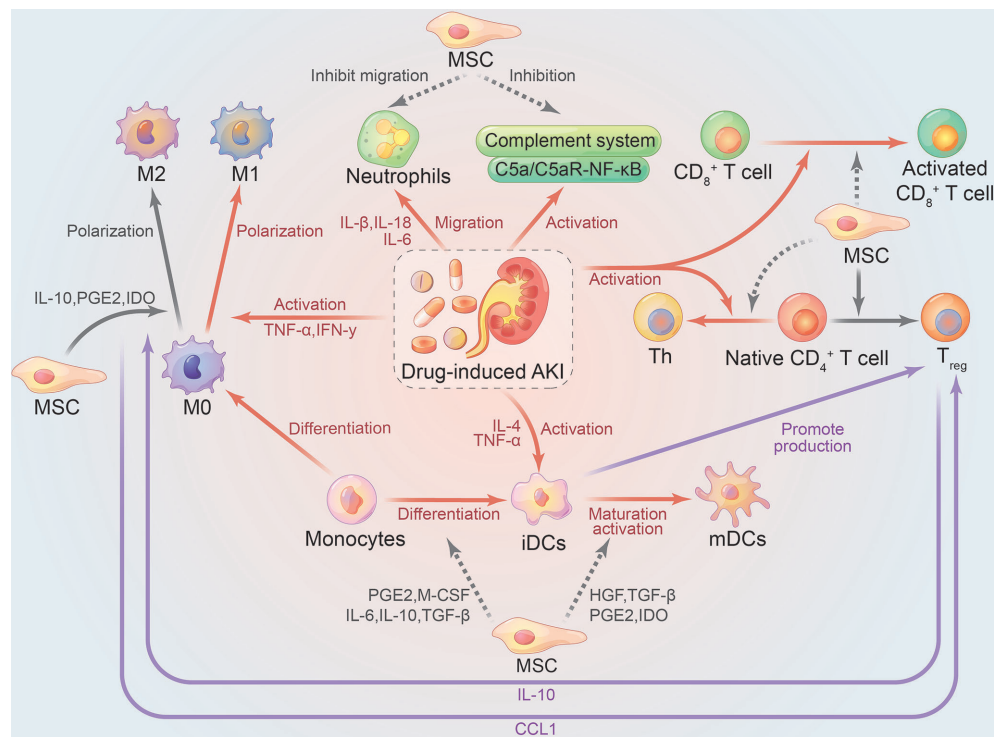
FIGURE 1 | Immunomodulatory effects of mesenchymal stem cells on drug-induced AKI. Gray, therapeutic effect of mesenchymal stem cells on the kidney; Red, damage effect of AKI on the kidney; Purple, interaction between immune cells; Solid line, promoting effect; dashed line, inhibiting effect. AKI, acute kidney injury; iDCs, immature dendritic cells; mDCs, mature dendritic cells; Th, helper T cells; Treg, CD3$^+$CD4$^+$CD25$^+$Foxp3$^+$ regulatory T cells; HGF, hepatocyte growth factor; IDO, indoleamine 2,3-dioxygenase; PGE2, prostaglandin E2; TGF-β, transforming growth factor β.

intermediates between endothelial and epithelial cells (21). In the injured state, renal DCs express specific cytokines through toll-like receptors, nod-like receptors, cell fragments, or other DAMPs, and present antigens to T cells to complete the transition from innate to adaptive immunity (57, 58). Similar to macrophages, DCs have two types: a pro-inflammatory phenotype (mature DCs; mDCs) and an anti-inflammatory phenotype (immature DCs; iDCs). Renal DCs are capable of immune induction and/or immune tolerance; thus, imbalanced immune regulation leads to the occurrence and progression of AKI. In cisplatin-induced AKI, IL-4 and TNF-α activate iDCs into mature phenotypes at the initial stage, causing kidney damage. IL-10, which is mainly derived from renal iDCs and plays an important role in immune regulation, has a nephroprotective effect and can reduce the nephrotoxicity of cisplatin in an inducible nitric oxide synthase-dependent manner (59). Hence, inhibition of nitric oxide synthase activity leads to a reduced number of IL-10-secreting DCs and loss of the renal protective effect of BM-MSCs (60). Furthermore, clearance of IL-10-secreting DCs can aggravate cisplatin-induced nephrotoxicity (52, 59). MSCs can inhibit the maturation of DCs and promote their transition to a tolerant immunosuppressive phenotype. They can also inhibit the differentiation of monocytes into iDCs by secreting PGE2, monocyte colony-stimulating factor, IL-6, IL-10, and TGF-β. Furthermore, MSCs can inhibit the maturation of iDCs into mDCs by secreting hepatocyte growth

factor, TGF-β, PGE2, and IDO (56). PGE2 can inhibit the production and secretion of osteopontin, a cytokine released from DCs, which contributes to tissue inflammation (61). In the inflammatory microenvironment, iDCs stimulated by IL-10 (produced by MSCs) fail to express markers of mDCs (62). These iDCs do not produce TNF-α and, thus, can inhibit the progression of inflammation at the site of injury (63, 64). In addition, iDCs can promote the production of Tregs and exert anti-inflammatory effects. Some studies have shown that MSCs reduce the expression of major histocompatibility complex class II, CD40, and CD86 costimulatory molecules by mDCs, which is the cause of the decrease in T cell proliferation and weaker immune responses (65). MSCs also inhibit the antigen-presenting effects of DCs on CD4$^+$ and CD8$^+$ T cells in inflammatory lymph nodes (66), and reduce the production of pro-inflammatory factors, such as interferon-γ and IL-17 (67). These immunomodulatory effects help to reduce cisplatin-induced kidney damage.

Neutrophilic Granulocytes

When AKI occurs, many neutrophils are transported and accumulate in the blood vessels of the kidney, leading to blockage of the microvascular network. With the help of endothelial chemokines and adhesion molecules, neutrophils are attracted to the damaged site, mediate inflammation, and assist in the elimination of damaged cells in preparation for the

repair of the kidney (68). However, this effect is a double-edged sword. If the inflammatory response is insufficient, damaged or dead cells cannot be cleared in a timely manner, resulting in delayed tissue healing and AKI may eventually develop into chronic kidney disease. However, if the inflammatory response is excessive, cytotoxic compounds (ROS, proteases, and inflammatory cytokines) secreted by neutrophils will adhere to the kidney endothelial cells in large quantities, which triggers inflammatory factor infiltration and impairs the cell repair processes. A study reported that neutrophil infiltration increased in a group of cisplatin-treated mice compared to the control group (25). Interestingly, when caspase-11 was inhibited, neutrophil infiltration decreased, suggesting that cisplatin can induce neutrophil infiltration *via* caspase-11 activation (69). Other ways to significantly reduce neutrophil infiltration after administration of cisplatin include the use of TNF-α inhibitors, TLR-4 antagonists, or anti-intercellular adhesion molecule-1 antibodies (53), thereby partially improving cisplatin-induced AKI. Studies have shown that when MSCs are used to treat AKI, the migration and infiltration of neutrophils in the kidneys, as well as the serum creatinine and blood urea nitrogen levels, are significantly reduced, and renal function and kidney pathological damage is ameliorated (31, 70).

Macrophages

The mononuclear-macrophage system plays a crucial role in the immune response. According to changes in the microenvironment at the injury site, macrophages can differentiate into pro-inflammatory (M1) or anti-inflammatory (M2) cell phenotypes, which play an important role in the stage of damage and repair, respectively (26). After acute renal tissue destruction, monocytes are immediately recruited to the damaged site and are stimulated by DAMPs and PAMPs (TNF-α, interferon-γ, saturated fatty acids, and IL-6) to differentiate into the M1 phenotype and participate in the innate immune response (71, 72). Additionally, through the production and secretion of various cytotoxic substances, such as chemokines, pro-inflammatory cytokines, and inducible nitric oxide synthase, M1 cells amplify the renal inflammatory response in AKI and exacerbate disease progression (50). However, blockage of macrophage recruitment does not completely prevent cisplatin-induced AKI (73). Some studies have shown that the M2 phenotype inhibits excessive inflammatory reactions by secreting anti-inflammatory mediators (such as IL-10 and TGF-β), and promotes renal cell repair (74, 75). MSCs therapy can significantly reduce cisplatin-mediated immune cell infiltration in damaged kidney tissues, such as macrophages, DCs, neutrophils, and CD4^{+} and CD8^{+} T cells. As a result, it inhibits the production of inflammatory factors, but stimulates the secretion of the anti-inflammatory factors IL-10, IL-6, nitric oxide, and kynurenine (60). In addition, MSCs can promote the differentiation of macrophages into the anti-inflammatory M2 phenotype by secreting various factors including PGE2, IL-10, and IDO (67). Furthermore, the M2 phenotype can secrete CCL1 to promote Treg production. Therefore, the anti-inflammatory effects of MSCs can be further improved, and the kidney damage caused by cisplatin can be ameliorated.

Complement System

The complement system plays an important role in innate immunity and is activated by either of three pathways: classical, alternative, or lectin pathways (76), which eventually lead to the cleavage of C5 into C5a and C5b. These two allergenic proteins later form the complement membrane in the first step of forming the attack complex. Studies have shown that N-acetylcysteine can reduce the nephrotoxic effect of cisplatin by inhibiting the binding of C5a to C5aR. In addition, inhibiting C5aR can reduce neutrophil infiltration and the effects of inflammatory factors (77). When MSCs were used to treat AKI, serum C5a levels and C5aR expression in renal tissues were significantly reduced, and NF-κB translocation was also reduced. Hence, MSCs can reduce AKI by inhibiting the activation of the C5a/C5aR–NF-κB pathway (27).

CONCLUSION AND PERSPECTIVE

To date, the safest route of administration of MSCs in clinical applications is through vascular injection; thus, the number of MSCs that can reach the kidney is very small (47). Several scientists have attempted to improve the efficacy of MSCs through various methods. Improving the immunomodulatory ability of MSCs is key to improving their therapeutic effect. Studies have been conducted to regulate the relevant immune responses by innovative pretreatment methods, thereby enhancing the kidney repairing effect (78, 79). Currently, most reviews focus on AKI due to ischemia-reperfusion. However, there are relatively few studies on drug-induced AKI, especially on the role of the complement system. Drugs-induced kidney injury is also one of the biggest causes of AKI (4). Future research in this area will help deepen our understanding of the immune regulation mechanism of MSCs therapy for AKI, and discover more potential therapeutic targets.

AUTHOR CONTRIBUTIONS

QH and XW had the original idea and wrote the first draft. HZ, JH, and GC reviewed the manuscript. HZ and XD provided critical input. All authors contributed to the article and approved the submitted version.

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