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REVIEW

The role of macrophage migration inhibitory factor on glucose metabolism and diabetes

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Abstract Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine involved in many inflammatory reactions and disorders, and it has become evident that it also affects glucose homeostasis. The protein is produced by pancreatic beta cells and can promote the release of insulin. It also modulates glucose uptake, glycolysis and insulin resistance in insulin target cells such as the adipocyte, myocyte and cardiomyocyte. Possessing both immunological and endocrinological properties, MIF has been associated with the development of type 1 and type 2 diabetes, and it may be important in the setting of islet transplantation. The present review summarises our current knowledge, based on clinical and research data, on the impact of MIF on both physiological and pathological aspects of glucose metabolism.

Keywords Cytokine · Diabetes · Inflammation · Islet transplantation

Abbreviations

ACTH	adrenocorticotropic hormone
ISO-1	3-(4-hydroxyphenyl)-4,5-hydro-5-isoazole acetic acid methylester
MCP-1	monocyte chemotaxis protein-1
MIF	macrophage migration inhibitory factor
PFK-2	6-phosphofructo-2-kinase
Th1	T helper cell type 1

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Macrophage migration inhibitory factor (MIF) was one of the first of the proinflammatory cytokines to be described. In the 1960s it was reported to inhibit the migration of macrophages in vitro [1, 2], with a maximum effect achieved at 80 pmol/l [3]. Its broad proinflammatory activities were more extensively described during the 1990s, following the elucidation of the DNA sequence for the protein (chromosome 22 in humans and chromosome 10 in mice), which led to the production of the recombinant protein [4–7].

Mif is known to be constitutively expressed in numerous types of tissue, such as lung, skin, the gastrointestinal and urinary tracts, several endocrine glands (pancreatic beta cells, ovary, testis, hypothalamus, adrenal and pituitary glands) and cells of the immune system (T and B cells, monocytes/macrophages, neutrophils, eosinophils, basophils, mast cells, dentritic cells) [8–13]. In addition, it is involved in various acute and chronic inflammatory diseases, including sepsis, adult respiratory distress syndrome, glomerulonephritis, arthritis, colitis and gastritis [14]. There is a close relationship between the role of MIF in the inflammatory/immune response and its role in glucose metabolism. Acute inflammation can lead to abnormal glucose regulation, while type 1 and type 2 diabetes are associated with chronic immune and inflammatory reactions [15].

Increasing evidence suggests that MIF plays a key role in glucose homeostasis during periods of stress and in the development of type 1 and type 2 diabetes. The present review describes the role of MIF in the immune response and its physiological and pathological effects on glucose metabolism, using both research and clinical data. In addition, potential sites for therapeutic regulation of MIF activity are explored.

Structural and signalling aspects of MIF

The normal range for plasma MIF is 0.2–0.5 nmol/l in humans [16]. The X-ray crystal structure of the protein, at a resolution of 2.6 Å [17], shows that this small (12 kDa) hydrophilic cytokine is composed of a trimer of identical subunits. The MIF receptor has been identified as the CD74–CD44 complex, which can be found on most nucleated cells [18–22], and the cytokine binds primarily to the extracellular transmembrane component, CD74. The CD44 component is required for the transduction of binding signals mediated by the p44/p42 mitogen-activated protein kinase (extracellular signal-regulated protein kinase 1/2) pathway [18, 22]. It should be noted that CD74 is also known as the MHC class II invariant chain, while CD44 is a recyclable receptor with an important role in cell–extracellular matrix interactions [23].

MIF and innate and adaptive immunity

The proinflammatory effect of MIF in the innate immune response has been extensively studied (see text box: Impact of MIF on innate and adaptive immunity and glucose metabolism, Fig. 1a). Endotoxin and various inflammatory cytokines, including TNF-α and IFN-γ (but not IL-1β and IL-6), increase *Mif* expression and the release of the protein by macrophages, while IL-10 inhibits its release [10, 24]. MIF activates macrophages in an autocrine and paracrine manner, generating a positive-feedback loop. It promotes the production of TNF-α, cyclooxygenase 2 and prostaglandin E_2, amplifying the inflammatory reaction [5, 10, 14, 25]. MIF also enhances the production of TNF-α and type 1 IL-1 receptors on various cells, as well as the production of Toll-like receptor 4 on macrophages [26–28].

When MIF has been released at a site of inflammation, it promotes the recruitment of more leucocytes, thus increasing the innate response and propagating an adaptive response. It increases the expression of the adhesion molecules vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which mediates monocyte adherence to the vascular endothelium located near the site of inflammation [29]. MIF binds to the chemokine receptors CXCR2 and CXCR4, thereby promoting monocyte and lymphocyte arrest in the area of inflammation [30]. MIF contributes to leucocyte transmigration from the vessels to the inflamed tissue by promoting endothelial cell production of monocyte chemotaxis protein-1 (MCP-1), a potent chemoattractant [31]. During the inflammatory response, the turnover of immune cells is elevated, in part due to activation-induced

Impact of MIF on innate and adaptive immunity and glucose metabolism

Innate immunity
- Released by monocyte/macrophages [10]
- Required for release of TNF-α, COX2, PGE_2 [10, 25, 97]
- Promotes the production of VCAM-1 and ICAM-1 by monocytes [29]
- Contributes to monocyte transmigration to tissues via MCP-1 [31]
- Binds to CXCR-2 and CXCR-4, and promotes monocyte and lymphocyte arrest in the area of inflammation [30]
- Promotes the production of Toll-like receptor 4 [26, 27]
- Promotes the production of TNF-α and IL-1 receptors [28]
- Decreases p53-mediated apoptosis in monocytes [25]
- Can override glucocorticoid-mediated inhibition of TNF-α, IL-1β, IL-6, IL-8 in monocytes [98]

Adaptive immunity
- Released by T lymphocytes (resting and stimulated) [33, 34]
- Promotes T and B lymphocyte proliferation, the release of IL-2 and the expression of the gene encoding the IL-2 receptor [33, 35, 36]
- Modulates the Th1/Th2 response [37-39]
- Can override glucocorticoid-mediated inhibition of IFN-γ, IL-2 in T lymphocytes [33]

Glucose metabolism
- Released by pancreatic beta cells, myocytes, cardiomyocytes and adipocytes [44, 46-51]
- Promotes the secretion of insulin by pancreatic beta cells [44]
- Contributes to glucose uptake and catabolism in muscle and heart [49, 52]
- Can decrease insulin signal transduction [51, 53]

COX2, cyclooxygenase 2; ICAM-1, intercellular adhesion molecule-1; PGE_2, prostaglandin E_2; Th1, T helper cell type 1; Th2, T helper cell type 2; VCAM-1, vascular cell adhesion molecule-1

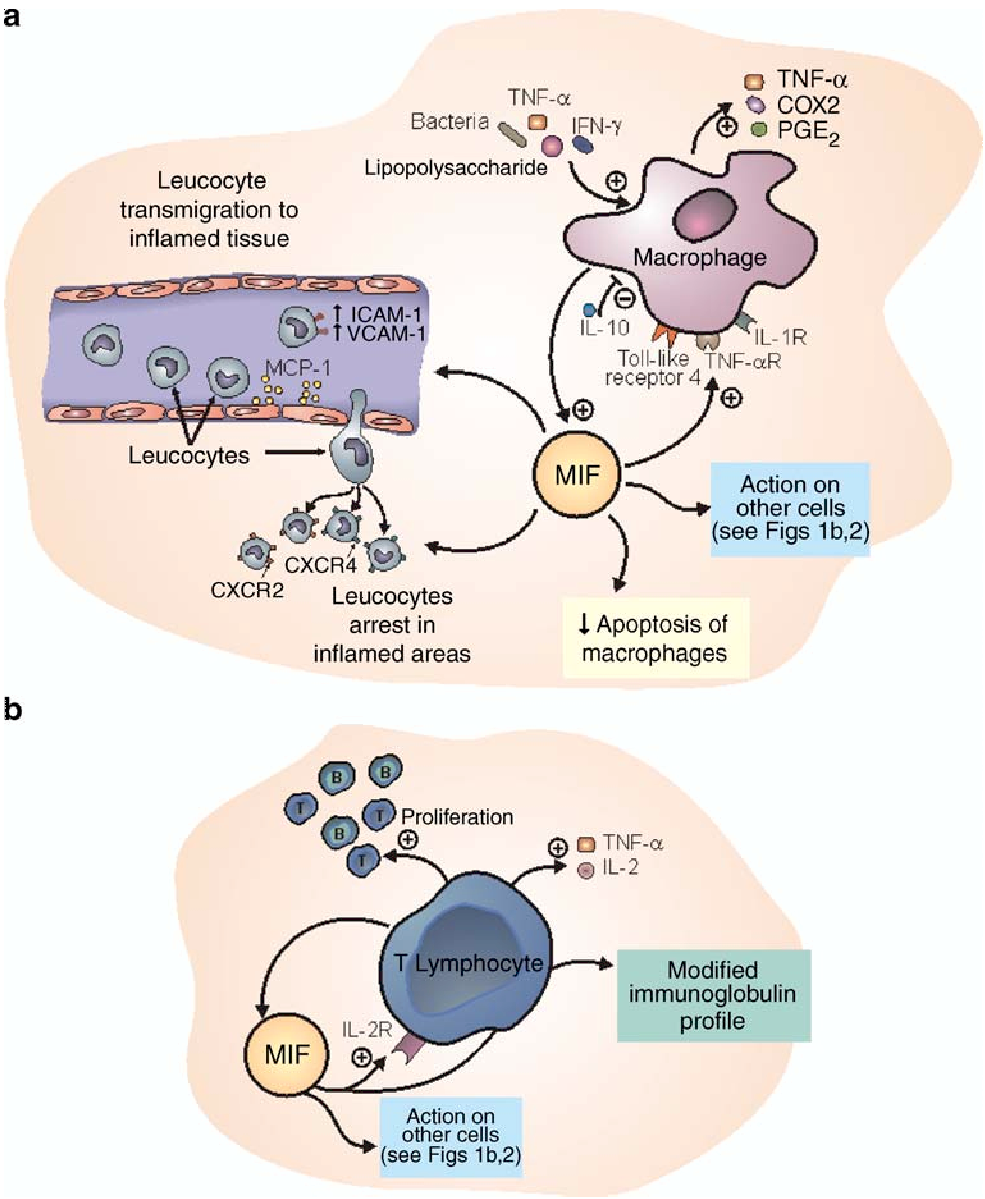

Fig. 1 Schematic diagrams of the known effect of MIF on innate **(a)** and adaptive **(b)** immunity. COX2, cyclooxygenase 2; IL-1R, IL-1 receptor; TNF-αR, TNF-α receptor

cell death (apoptosis). MIF maintains the inflammatory response by decreasing p53-mediated lymphocyte apoptosis and improving macrophage survival [25, 32].

Several recent articles suggest that MIF plays a significant role in the adaptive immune response (Fig. 1b). MIF is secreted by T lymphocytes under normal conditions and is increased in response to various proteins, including anti-CD3, phorbol 12-myristate 13-acetate (PMA) and concanavalin A, all of which are potent in vitro lymphocyte stimulators [33, 34]. Similar to its effects on macrophages during an innate response, MIF has an autocrine effect on lymphocytes. It promotes the release of IL-2 and TNF-α, the expression of the gene encoding the IL-2 receptor (CD25), and, ultimately, the activation and proliferation of T and B cells [33, 35, 36]. MIF affects the balance between T helper cell type 1 (Th1) and Th2 responses and alters the type of immunoglobulin secreted by B cells [37–39]. However, the impact of MIF on the Th1 vs Th2 pathway appears to be dependent upon the disease process involved [37–39]. It remains unclear whether MIF modulates the secretion of immunoglobulin directly or indirectly through mediators. MIF also contributes to cytotoxic activity against tumour cells [34] and is involved in the delayed-type hypersensitivity reaction [40–42].

MIF and glucose metabolism

Besides its known role in the immune response, MIF influences glucose metabolism at several levels, affecting

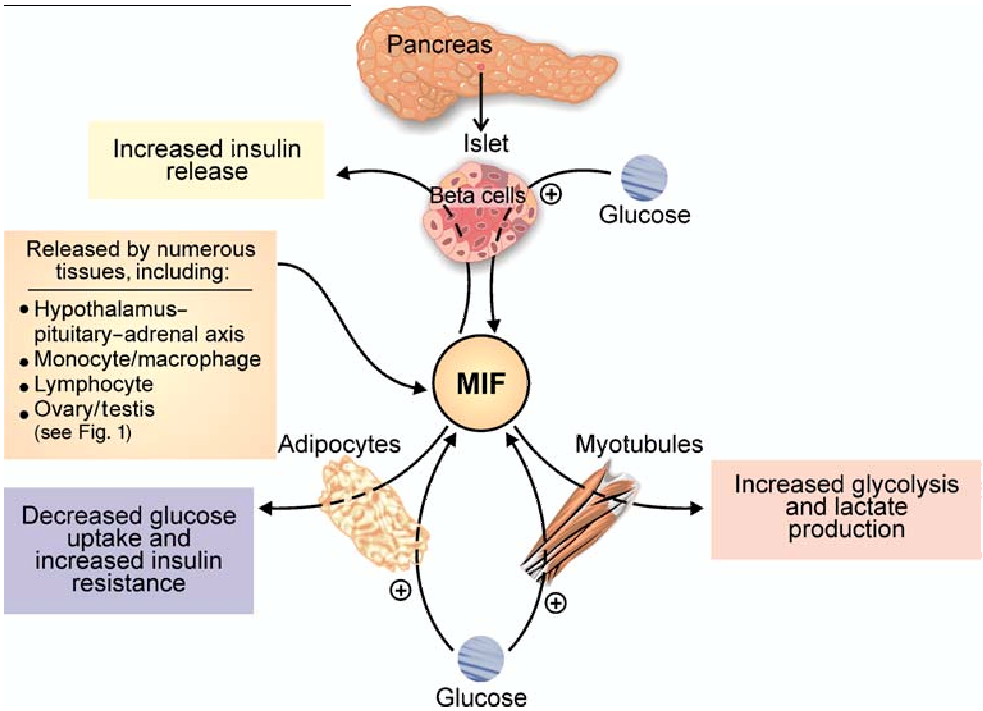

Fig. 2 Schematic diagram of the known impact of MIF on glucose metabolism

both insulin production in the pancreatic beta cell and the cells targeted by insulin (see text box: Impact of MIF on innate and adaptive immunity and glucose metabolism, Fig. 2) [15]. MIF is produced in beta cells and is co-localised with insulin in the secretory granules [15]. The expression of *MIF* within the beta cell and its plasma levels follow a circadian rhythm, with higher levels reported during the day [16, 43]. Its production is regulated by glucose in a time- and concentration-dependent manner [44, 45]. Once released, MIF has a positive autocrine action on insulin secretion, which ultimately leads to lower levels of glucose and MIF [44]. These observations are based on the increased glucose-induced insulin release from rodent islets in the presence of recombinant MIF in vitro [44]. In addition, the use of anti-MIF neutralising antibodies or the downregulation of *Mif* expression decreases glucose-induced insulin secretion in perifusion studies performed with rat islets or an insulin-producing cell line (INS-1) [44].

MIF is also produced by cells targeted by insulin, including myocytes, cardiomyocytes and adipocytes, both constitutively and in response to stimuli such as TNF-α [46–52]. Its release from adipocytes appears to be site-specific, as adipocytes from the subcutaneous tissue and the omentum secrete approximately ten times more MIF than mammary adipocytes [50]. MIF has an autocrine/paracrine effect on adipocytes, and has been suggested to mediate the effects of TNF-α on glucose catabolism, specifically in the context of stress [51]. MIF also induces enhanced glucose uptake and glycolysis in muscle, as assessed by higher levels of the enzyme 6-phosphofructo-2-kinase (PFK-2), which is associated with an increase in the synthesis of fructose 2,6-biphosphate, a powerful positive allosteric regulator of glycolysis, further leading to enhanced lactate production [49]. Experiments on mouse heart metabolism have suggested that MIF exerts its metabolic effects at least in part via the AMP-activated protein kinase pathway [52], which acts as a sensor of the energy state of the cell and induces diverse signals to increase ATP production. This can result in a rise in glucose uptake following increases in the translocation of GLUT4 to the cell surface and PFK-2 activity, leading to a higher rate of glycolysis [52]. As a consequence of the MIF-mediated metabolic effects, and in contrast to wild-type controls, MIF knockout (KO) animals or mice treated with anti-MIF neutralising antibody exhibit normal blood glucose levels, lactate response and liver glycogen content following the administration of endotoxin or TNF-α [49, 51]. In addition, MIF KO animals or mice treated with neutralising anti-MIF antibody demonstrate a selective increase in insulin-mediated glucose uptake into white adipose tissue after TNF-α treatment, while glucose uptake in skeletal muscle and brown adipose tissue and hepatic glucose production are not affected [51]. MIF is a necessary mediator of TNF-α inhibition of the insulin signal transduction leading to insulin resistance [51, 53]. This effect is related to reduced phosphorylation of the protein kinase Akt, which together with a phosphatidylinositol 3-kinase, is necessary for phosphorylation of IRS-1, a secondary messenger of the insulin receptor involved in stimulating the transcription of insulin-regulated genes [51].

MIF and stress

MIF has been extensively studied as a mediator of the response to stress in humans [54]. Very high serum levels of MIF (up to tenfold above normal range) can be found in patients suffering from various insults, including major surgery (liver resection), systemic inflammatory response syndrome, severe sepsis or septic shock. Higher levels are also seen in patients who ultimately die [55–57].

Several animal models have further confirmed the role of MIF in the setting of stress [58]. MIF is produced at all levels of the hypothalamic–pituitary–adrenal axis, but pituitary production is the most striking [59]. In the pituitary gland, MIF is located in the secretory granules of the corticotropic cells, which also contain adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone [60, 61]. The expression of *Mif* and release of the protein are induced by corticotropin-releasing hormone [60, 62], and MIF levels are inversely correlated with the adrenal response, as reflected by low levels of serum cortisol and increased levels of ACTH following MIF release [57]. In contrast, cortisol induces MIF production from various tissues, including the adrenal gland [63].

In mouse models of septic shock, intracellular stores of MIF are released from various tissues (pituitary, adrenal, lung, liver, spleen, kidney and skin) within a few hours, with the *Mif* transcriptional response seen later [59]. Following such an event, the pituitary content of MIF is decreased. MIF appears to play a central role in stress, as its administration leads to an increased mortality rate, whereas anti-MIF neutralising antibodies or the absence of MIF can protect mice from shock and death [64, 65].

Stress is typically characterised by an increase in the cellular uptake of glucose and an increase in the production of glucose by the liver. During the first phase, the increased insulin resistance leads to some degree of hyperglycaemia [66]. However, hypoglycaemia subsequently occurs, probably as a result of an inappropriately high level of insulin secretion and inhibition of glucose production by the liver [67]. The depletion of MIF can normalise the blood glucose and lactate response following TNF-α- and lipopolysaccharide-induced stress in mice [51].

MIF and type 2 diabetes

Several lines of clinical evidence support a relationship between MIF and type 2 diabetes. Serum concentrations of MIF are higher in patients with type 2 diabetes than in patients with impaired glucose tolerance (as assessed by an OGTT), who have higher levels than healthy individuals [68–70]. In addition, metabolic tests performed on Pima Indians, an ethnic group prone to type 2 diabetes, have demonstrated a link between MIF and insulin resistance [69]. The association of type 2 diabetes with MIF appears to be strong and closer than that with other proteins, such as C-reactive protein and IL-6 [70].

Interestingly, blood concentrations of MIF are not uniformly distributed between sexes. In a recent large case-cohort study, elevated serum levels of MIF were associated with a higher risk of type 2 diabetes in women (HR 1.74) but not in men [71]. Another factor that may explain the variability of *MIF* expression in the population is the finding that a number of different *MIF* promoter genotypes have been identified [72, 73]. For example, a common polymorphism containing between five and eight CATT tetranucleotide repeats (−794 $CATT_{5–8}$) demonstrated a reduced *MIF* promoter activity [72]. Similarly, the observed difference in serum levels of MIF between male and female patients with type 2 diabetes has been linked to specific single nucleotide polymorphisms (rs2070767, rs1007888) in the *MIF* gene [71]. Besides these genetic variations, the difference between sexes may reflect the influence of sex hormones on MIF at the transcriptional level. For instance, it has been shown that oestrogens can regulate MIF production from mouse and human monocytes and macrophages through the important transcriptional regulator nuclear factor κB [74]. This sex specificity is in line with similar observations regarding body composition, serum markers of inflammation and the risk of type 2 diabetes [75].

Serum MIF is correlated with BMI [76], with higher serum protein levels and an increased frequency of certain *MIF* variants observed in obese individuals [71, 77, 78]. This is supported by the observation that adipocytes from obese donors tested ex vivo secrete higher levels of MIF than adipocytes from non-obese donors [50]. Interestingly, treatment of obese individuals with normal blood glucose levels with metformin (1000 mg orally twice daily) resulted in a significant decrease in plasma MIF concentrations [76]. Similarly, obese individuals participating in physical activity and following a dietary-focused management programme also demonstrated decreased plasma levels of MIF [77]. While obesity is associated with a chronic inflammatory response, MIF is only one of many cytokine mediators, such as TNF-α, IL-1β, IL-6, IL-8, IL-10, TGF-β and nerve growth factor, to be involved in this response [79]. As such, the causal relationship between obesity and MIF production has not been firmly established as yet. In addition, the increased secretion of MIF may originate from various cells and tissues. For example, mononuclear cells of obese individuals demonstrate higher levels of MIF [76].

These clinical studies demonstrate a strong relationship between MIF and type 2 diabetes. However, it has yet to be determined whether increased MIF levels lead to disease development or are instead secondary to type 2 diabetes. Interestingly, a preliminary report suggested a causal effect

of MIF [80]. MIF KO mice demonstrated an age-dependent significant weight gain, together with elevations in glucose levels and insulin release following an intra-peritoneal glucose challenge. This type 2 diabetes-like pattern may suggest a central role of MIF in the disease, but further investigations are needed before any conclusions can be drawn.

MIF and type 1 diabetes

MIF levels are lower in patients with recent-onset type 1 diabetes who have multiple autoantibodies (anti-GAD, anti-insulinoma-associated antigen-2, anti-islet cell antibodies). While classical Th1/Th2 cytokines (IFN-γ, IL-5, IL-10, IL-13) are not affected, decreased levels of MIF, together with decreased MCP-1 and increased IL-18, can predict autoantibody positivity with 85% sensitivity and 94% specificity [81]. Interestingly, MIF and MCP-1, usually associated with the innate pathway, are also known to be produced by pancreatic islets [44, 82]. As such, the decrease in these islet-produced hormones could reflect a modification in overall immune activity and/or be associated with decreased islet secretion, which is potentially linked to diabetic injuries. It remains unclear how serum MIF levels of patients with type 1 diabetes compare with those in healthy individuals.

Several lines of experimental data suggest a key role for MIF in the development of autoimmune diabetes. The expression of *Mif* and release of the protein are increased in both pancreatic islets and peripheral lymphocytes of animals with autoimmune diabetes [83, 84]. In addition, in NOD mice treated with recombinant MIF protein (25 μg i.p. twice a week from 6–11 weeks of age) the incidence of diabetes is increased from 55% to 86% [84]. Consistent with this, several animal experiments have demonstrated that anti-MIF antibody and knockout of *Mif* could prevent autoimmune diabetes in mice [39, 83]. These observations are specific to autoimmune models of diabetes, since no protective effect was observed after chemical induction of diabetes with a standard dose of streptozotocin i.p. in C57BL/6 mice [83]. Taken together, these results from various animal models suggest a central role for MIF in the development of autoimmune diabetes.

Antagonising the action of MIF has a profound effect on various immune parameters. In mouse models of autoimmune diabetes, the production of proinflammatory mediators in splenic mononuclear cells (TNF-α, IL-1β, IL-12, IL-23, IFN-γ and nitric oxide) and islets (TNF-α, IL-18, IL-1β, and iNOS) is decreased [39, 83]. In contrast, the levels of IL-4, TGF-β and IL-10 are increased, demonstrating an overall immune deviation towards a protective type 2 response. Anti-MIF therapy also leads to decreased expression of the IL-2 receptor on the surface of splenocytes and a lower rate of proliferation of lymphocytes in vitro. These observations suggest that MIF contributes to the clonal expansion of T cells during autoimmune diabetes [39, 83]. Resistance to autoimmune diabetes in MIF KO animals may also be related to observed decreases in susceptibility to injury and apoptosis [85]. These animals also demonstrate lower levels of production of IL-1β [85].

Overall, these observations suggest that anti-MIF strategies can prevent autoimmune diabetes in mice. While this represents a very important preliminary step, it should be noted that these animal models only approximate the human disease. The demonstration of the efficiency of a treatment in mice is therefore not a guarantee of success in humans.

Besides type 1 diabetes, MIF may also play a role in other less common variations of the disease. This is the case for MODY3, which is caused by heterozygous mutations in the gene encoding hepatocyte nuclear factor-1α (*HNF1A*) and is characterised by impaired insulin secretion. INS-1 cells engineered to overexpress *HNF1A* containing a mutation associated with MODY3 in humans showed impaired growth and decreased expression of *Mif* [86].

MIF and islet transplantation

The impact of MIF on the allogeneic immune response in transplantation is controversial. MIF production is upregulated in cases of kidney or heart graft rejection, as demonstrated by animal and human studies [87–89]. Neutralising anti-MIF antibodies can inhibit indirect allorecognition of skin grafts, probably partly through inhibition of macrophages [41]. Blockade of MIF production with a liposome-transfected small interfering RNA prevented early obstructive bronchiolitis and destruction in a mouse tracheal allograft model [90]. Conversely, murine cardiac and renal allograft rejections were not prevented or even delayed in MIF KO recipients or by use of anti-MIF neutralising antibodies [42, 89].

The challenges linked to islets differ from those related to solid organ transplantation. First, pancreatic islets produce MIF [44, 45, 91], which can have a local impact at the site of islet implantation. Microarray studies have demonstrated that *MIF* is one of the most strongly expressed genes in human islets in culture [91]. Furthermore, islet transplantation involves the early loss of many islet cells (50% or more), owing to poor engraftment. Several factors may induce these events, including the activation of the coagulation cascade, which is responsible for non-specific inflammatory reactions [92]. Several mediators, including MCP-1, IFN-γ and IL-1β, have been associated with lower islet isolation yields and impaired post-transplantation islet function [82, 93]. Based on these findings, one can postulate that MIF is involved in a similar deleterious process. This hypothesis is supported by a report of decreased in vitro cytokine-induced death in MIF-depleted islets [85].

Finally, since islet transplantation is most often performed in patients with type 1 diabetes, some patients will develop a progressive recurrence of autoimmunity to the islet graft [94]. Since MIF plays a role in the development of autoimmune diabetes in animal models, it is possible that an intervention aiming at inhibiting MIF secretion may also improve the long-term survival of the islet grafts. Potential strategies include the use anti-MIF antibodies or molecular inhibitors such as the recently developed 3-(4-hydroxyphenyl)-4, 5-hydro-5-isoazole acetic acid methylester (ISO-1) [95, 96]. These strategies remain to be tested in the setting of islet transplantation.

Summary and future directions

MIF is an important mediator involved in numerous immuno-inflammatory disorders and pathways. For this reason, many efforts have been made to develop neutralising strategies that can potentially be applied to humans [96]. The use of neutralising anti-MIF antibody has proven to be efficient in several animal models, including septic shock, arthritis, multiple sclerosis (experimental autoimmune encephalomyelitis) and asthma [96]. Chemical inhibitors such as ISO-1 or COR100140 have also been developed and tested in animal models of inflammatory disorders [96]. The modes of action of these compounds still remain to be fully elucidated and their side effect profiles better characterised, but they may be interesting tools for future interventions on diabetes.

With its dual proinflammatory and metabolic effects, MIF represents a logical focus of study in the field of diabetes. An association between type 2 diabetes and MIF appears clear, with higher plasma MIF levels observed in affected individuals than in healthy controls [70, 71]. While type 2 diabetes is associated with obesity, and is itself related to higher circulating levels of many proinflammatory cytokines, the main challenge will be to determine whether a causal relationship exists between MIF and type 2 diabetes. If this were proved to be the case, a new therapeutic target could be developed. In murine models of type 1 diabetes, the inhibition of MIF modulated the immune response involved in the disease and maintained stable blood glucose levels [39, 83]. These experiments demonstrate a direct causal role of the cytokine in this autoimmune disease. While important, the mechanisms associated with these observations remain to be fully characterised.

Although MIF appears to be a potential therapeutic candidate for these diseases, one must keep in mind the various, sometimes diverging metabolic effects of this cytokine. Besides modulating the immune response and preventing the inflammatory response, inhibition of MIF has the potential to improve the glucose profile by decreasing peripheral insulin resistance [51, 53]. Conversely, MIF inhibition could decrease insulin release from pancreatic beta cells and glucose uptake and glycolysis in muscle and heart.

Overall, the balance between positive therapeutic effects and potential side effects of a MIF-targeting intervention need to be better understood. However, recently, an increasing number of studies have focused on MIF, which has emerged as an important player in the physiological and pathological regulation of glucose metabolism. Taken together, the data reported to date are promising and should encourage further exploration in this field.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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