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REVIEW

Macrophage Migration Inhibitory Factor (MIF): Biological Activities and Relation with Cancer

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Abstract Macrophage migration inhibitory factor (MIF) emerged in recent years as an important inflammation mediator, playing a prominent role in the pathogenesis of various types of malignant neoplasm. MIF is a glycoprotein that presents a wide spectrum of biological activities and exerts a complex interaction with various cellular signaling pathways, causing imbalance of homeostasis. Experimental and clinical studies show that high levels of MIF are found in almost all types of human cancers and are implicated in seemingly all stages of development of the tumors. The production of MIF is triggered through an autocrine signal emitted by tumor cells, and stimulates the production of cytokines, chemokines, and growth as well as angiogenic factors that lead to growth of the tumor, increasing its aggressiveness and metastatic potential. MIF is produced by virtually all types of human body cells, in response to stress caused by different factors, leading to pathological conditions such as chronic inflammation and immunomodulation with suppression of immune surveillance and of immune response against tumors, angiogenesis, and carcinogenesis. In this review, we present recent advances on the biological activity of MIF, the signaling pathways with which it is involved and their role in tumorigenesis.

Keywords Macrophage migration inhibitory factor · Neoplasms · Tumorigenesis · Inflammation

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Introduction

Macrophage migration inhibitory factor (MIF) was originally identified as a product isolated from the supernatants of activated T lymphocyte culture and was characterized as a cytokine capable of inhibiting the random migration of macrophages, being one of the first to be described [1]. Currently, MIF is considered a multifunctional molecule that activates the production of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interferon (IFN-γ). Also, it acts as an immunomodulator hormone produced by the pituitary gland, induced by glucocorticoids [2–4].

MIF is constitutively expressed in a variety of cells, its tissue distribution is almost ubiquitous, and its release into the circulation seems to occur from preformed stocks and stored in the intracellular environment [5–7].

MIF may exert its biological effects on cells through different cell signaling pathways (Fig. 1).

The binding of MIF to its CD74 receptor, in the presence of a signaling complex consisting of CD44, and a tyrosine kinase, Src, mediates a cascade of events leading to phosphorylation of ERK-1/2 [8], activating various effector proteins involved in the inflammatory response [9]. MIF is also a noncognate binder of the chemokine receptors CXCR that

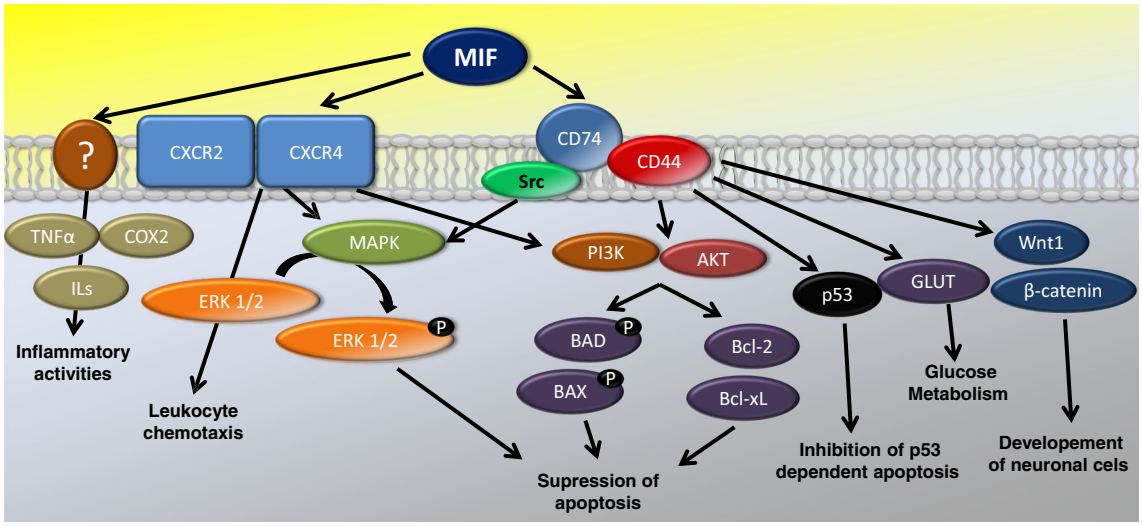

Fig. 1 Signaling patways regulated by the Macrophague Migration Inhibitory Factor (MIF). The arrows indicate the described relationships between MIF and the schematized intracellular pathways

directly binds them both, CXCR2 and CXCR4, and formation of the signaling complexes involving CXCR2 and CD74, that induces internalization of the receptors and stimulates leukocyte chemotaxis [10].

The binding of MIF to its receptor, CD74, also leads to activation of the AKT pathway through the mediation of kinases SRC and PI3K [11]. This activation leads to numerous cellular responses but, more importantly, AKT activation provides a signal, allowing the crucial cells to be capable of resisting apoptosis, due to phosphorylation and inactivation of the pro-apoptotic proteins BAD and BAX [11]. In lymphoid cells, activation of AKT induced by MIF is associated with increased NF-kB function, leading to increased expression of proteins Bcl-xL and Bcl-2 and suppression of apoptosis [12].

Previous research found that MIF is capable of activating cells of the immune system by acting directly on them or acting indirectly by generating other stimuli to the immune system. Thus, MIF is important in the activation of innate and adaptive immune responses, but also activates specific mechanisms which cause damage to the tissues. Due to its action on the immune-inflammatory response, MIF has the potential to trigger inflammatory and autoimmune diseases that affect multiple organs [13, 14].

The human MIF gene is located on chromosome 22q11.2 and encodes a highly conserved protein containing 115 amino acids. It is produced by a variety of cell types in response to stress [15], being considered a key regulator of the immune and inflammatory responses [16]. The gene expression is regulated by two polymorphic sites located in the promoter region. The first consists of a repetition CATT in −794 positions, which is represented 5–8 times, and the second is a single nucleotide polymorphism -173G/C [9]. The presence of more than 5 repeat of CATT, and of allele -173C, has been associated with increased susceptibility to and severity of a variety of inflammatory and autoimmune diseases [17–19]. It has also been associated with increased risk for prostate cancer [20] and gastric cancer [21].

MIF is also associated with the development of various types of inflammatory, lymphoproliferative, and autoimmune disorders [22] and is expressed in almost all stages of development of a wide variety of human cancers [23]. Furthermore, it may have a multifunctional role in human cancer since it exerts auto- and paracrine effects on cancer cells, promoting cell proliferation, growth, progression, and immune escape of tumor; inducing angiogenesis and migration of cells; and suppressing apoptosis and autophagy in tumor cells [24, 25].

The present review presents recent advances about biological activities of MIF and its participation in the activation of several cell signaling pathways, including its role in the promotion, progression, and invasion of several types of human cancers.

Biological Activities of MIF

MIF is a pluripotent and pleiotropic cytokine, which plays critical roles in inflammatory and immune responses, as well as in the development of tumors. It assists macrophages in carrying out functions such as phagocytosis, adherence, motility, and transendothelial migration. Besides, it is implicated in almost all stages of the development of neoplasia and its presence in high levels expression is a common feature of most types human cancer [23].

MIF is constitutively expressed in a variety of immune and non-immune cells such as eosinophils, neutrophils, granulocytes, and monocytes/macrophages, B and T lymphocytes, and endocrine, endothelial, epithelial, and neuronal

cells of different histogenetic origin, in response to the stress situations [7], being considered a key regulator of the immune and inflammatory responses [16]. In the nervous system, MIF is constitutively expressed in neurons within the hypothalamus, cortex, and hippocampus and has been implicated in different roles, including the modulation of nitric oxide and prostaglandin production, a stimulatory role in catecholamine metabolism, and the regulation of neuronal sensitivity to glucocorticoids [26].

MIF plays a central role in the etiology of various types of inflammatory and autoimmune disorders. It is found in high levels of expression in all stages of almost all types of human cancers, being strongly associated with the development of tumors [22]. The production of MIF, through autocrine signaling of tumor cells, stimulates the production of cytokines, chemokines (including MIF itself), and angiogenic and growth factors, whose expression is associated with inhibition of the induction of p53-dependent apoptosis and of the antitumor immune response [27, 28] . Thus, MIF contributes to cancer cell proliferation, for growth and progression of the tumor, increasing its aggressiveness and metastatic potential [23].

In addition to its role as a cytokine and chemokine, MIF also functions as a hormone, being secreted alongside ACTH, by the pituitary gland in response to stressors such as endotoxinaemia, and acts by regulating the anti-inflammatory and immunosuppressive activities of glucocorticoids, enabling the activation of the inflammatory and immune responses. Under conditions of stress, such as hypoxia and redox potential, MIF causes many changes to take place in the increased expression of genes such as those of the erythropoietin (EPO), glucose transporters (GLUT), vascular endothelial growth factor (VEGF), and matrix metalloproteinase (MMPs). All these changes are caused by up-regulation of hypoxia-inducible factor 1 (HIF-1) [9]. MIF is also implicated with an increase of expression of gene encoders of nitric oxide and cyclooxygenase-2 (COX-2) [29].

MIF also exhibits enzymatic thiol protein oxidoreductase and phenylpyruvate tautomerase activities [30]. Furthermore, it induces the production of derived myeloid cells (MDSCs) with suppressive action of T and NK cells [31], which together with tumor-associated macrophages (TAMs) lead to a strong suppression of the functions of these cells [32].

To perform its functions, MIF needs to interact with a wide variety of chemical mediators and other molecules, through a complex network of events that involve the activation of several cell signaling pathways, showing their great diversity of biological activities. Described below are some of the biological activities of MIF, which are also presented in summary form in Table 1.

Inflammatory Activities

The physiological role of MIF is to act to counterbalance the profound inhibitory effects of steroids on the inflammatory and immune responses [33]. MIF is a cytokine inducing inflammation that, when produced, stimulates the release of other cytokines, such as TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and IL-12, from macrophages triggering a strong inflammatory response [3]. Glucocorticoids are endogenous anti-inflammatory steroids that are synthesized in response to stress or injury, in part to regulate inflammation. MIF has glucocorticoid-antagonist action and acts as a pituitary hormone to counteract the anti-inflammatory and immunosuppressive activity of glucocorticoids produced by the adrenal

Table 1 Biological activities of MIF and their mechanisms of action

MIF activities	Mechanisms of action
1. Inflammatory cytokine	Modulates the expression of activators of inflammation such as nitric oxide COX-2, PGE2 and TLR4, with recruitment of inflammatory cells.
2. Chemotactic chemokine	Induces rolling, adhesion of leukocytes to vessel wall, and transendothelial migration of these cells.
3. Hormone activity	Acts as a glucocorticoid-antagonist, by suppressing its anti-inflammatory effects, to regulate inflammatory and immune responses.
4. Enzymatic activity	Converts D-dopachrome in 5,6-dihydroxy-2-carboxylic acid and acts as a phenylpyruvate tautomerase, using phenylpyruvate and p-hydroxyphenylpyruvate as substrates.
5. Deregulation of the cell cycle	Prepares the cell to bypass the cell cycle arrest and the death induction by apoptosis mediated by p53.
6. Immune suppression	Suppresses the antitumor immune surveillance by inhibition of cytotoxicity of NK cells and CD8 + lymphocytes.
7. Growth and differentiation of neuronal cells	Acts by activating the signaling pathway Wnt/β-catenin, increasing the activity β-galactosidase and by promoting NSPC differentiation.
8. Tumorigenic activity	Stimulates proliferation of tumor cells and tumor growth by activation of various signaling pathways, inhibits apoptosis and immune response, and increases VEGF.
9. Angiogenesis induction	Induces secretion of pro-angiogenic factors bFGF and VEGF favoring formation of blood vessel
10. Contribution to metastasis formation	Reduces the expression of E-cadherin and increased expression of matrix metalloproteinases, favoring metastasis.

glands, which results in the activation of the inflammatory and immune response [4, 34].

MIF also acts in modulating the expression of several other pro-inflammatory molecules, including MIF itself, nitric oxide, and cyclooxygenase 2 (COX-2) [29], thus creating an inflammatory environment, which leads to a significant increase in COX-2 production, which in turn increases production of prostaglandin 2 (PGE2), which also has inflammatory activity, generating positive feedback to the inflammatory response [35]. Moreover, MIF plays a critical role in the regulation of the innate immune response, through the pattern recognition receptor modulation, such as TLR4. Activation of TLR4 results in the production of pro-inflammatory mediators, including MIF, which induces the recruitment of inflammatory cells, among them neutrophils [36].

Chemotactic Activities

Although MIF was first identified as an inhibitor of macrophage migration, subsequent studies revealed that in the presence of inflammatory mediators, it is also capable of inducing leukocyte rolling, adherence, and transmigration of these cells [36]. MIF may exert a chemokine-like function (CLF) by interacting with the chemokine receptors CXCR4 and CXCR2 to promote the recruitment of inflammatory cells. MIF triggered Gα-i-and integrin-dependent arrest and chemotaxis of monocytes and T cells, by interacting with the chemokine receptors, CXCR2 and CXCR4, to promote rapid integrin activation and calcium influx [37].

MIF acts as a chemokine, promoting the adhesion of monocytes to the vessel wall and their transendothelial migration, where every step of recruitment of these cells is carefully controlled. This immobilization of monocytes to the endothelial surface is mediated by the action of chemokines that prevents bearing these cells, where the CXCR2 chemokine receptor plays an important role in this process. The CXCR2 and their ligands CXCL1 and CXCL8 play a critical role in mobilizing and arresting monocytes to the vessel wall. However, the CXCR2 receptor is also able to interact with many binders of the CXC subfamily and with MIF, which structurally does not belong to this sub-family, but functions as a non-cognate binder to CXCR2, acting as a chemokine playing a critical role in recruiting and arresting monocytes to the vessel wall [10].

Hormone Activity

The hypothesis that MIF might be a hormone produced in stress situations has been validated in an experimental study conducted by Nishino et al., (1995) [38]. Using animal models, these authors have detected the presence of MIF within of granules found exclusively in pituitary gland cells that secrete both adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH). It was found a subset of granules containing MIF and ACTH, or MIF and TSH. The amount of MIF-pituitary present within the granules decreased significantly after endotoxemia, showing that under stress conditions, the contents of the granules are released for circulation [38]. Thus, MIF appears to be a pituitary mediator to act as an anti-glucocorticoid natural hormone, exercising its regulatory action within the immune system. MIF seems to act on the inflammatory site to neutralize the inhibitory effects of the steroid hormones on the primary immune response to be mounted to eliminate the source of infection or tissue invasion [33]. Thus, MIF is considered a pluripotent pro-inflammatory cytokine with pleiotropic functions including inhibition of migration, anchoring of the macrophages, and counteraction of the anti-inflammatory and immunosuppressive activity of glucocorticoids [39].

The traumatic spinal cord injury activates the hypothalamic-pituitary-adrenal axis, a potent neuroendocrine regulator that in conditions of stress causes a deep, systemic and sustained intraspinal inflammatory response. Together, stress hormones and inflammatory mediators affect the growth and survival of neural and non-neural cells and the neurologic recovery. Glucocorticoids are endogenous anti-inflammatory steroids, produced in response to stress or injury, partly to regulate inflammation. In this context, acting as a pituitary hormone, MIF negatively regulates steroid production, suppressing the anti-inflammatory action of these hormones produced by the adrenal glands, resulting in the worsening of the traumatic spinal cord lesions. Thus, the use of inhibitors of MIF may provide a therapeutic advantage in the treatment of these lesions [4].

Enzymatic Activity

Interestingly, it has been demonstrated that MIF has at least two distinct catalytic activities, keto-enol tautomerase and thiol-protein oxidoreductase; therefore, it has been termed a "cytokine with enzymatic properties, or cytozyme" [30, 40].

The first hypothesis about possible MIF enzyme activity emerged when Suzuki et al. (1994) [41] found the structural similarity of this molecule to the bacterial isomerase enzyme, specifically 5-carboxymethyl-2-hydroxymuconate (CHMI). However, the enzymatic activity of MIF was first described when Rosengren et al. (1996) [42] reported the tautomerase-D-dopachrome (DOPD) activity. They found that MIF has the ability to convert D-dopachrome in 5,6-dihydroxy-2-carboxylic acid (DHICA). Other studies have shown that MIF can also act as a phenylpyruvate tautomerase, using phenylpyruvate and p-hydroxyphenylpyruvate as substrates [43] and as thiol-protein oxidoreductase [44]. Furthermore, it was found that MIF is capable of catalyzing the conversion of 3,4-hydroxyphenylaminechrome and norepinefrinecromo, toxic quinine products of the neurotransmitter catecholamine

3,4-dihydroxyphenylamine and norepinephrine, to indoledihydroxy derivatives that may serve as precursors to neuromelanin [45].

In addition, it was postulated that MIF has a stake in the detoxification process of degradation products of catecholamine and may play a role in protection of nerve tissue. However, the exact role of this enzymatic activity of MIF in clinical disease has not been clearly defined, since many of the substrates defined for this enzyme do not naturally exist in vivo or do not exist in concentrations required for biological activity [46]. However, because of the great importance of MIF activity in diseases of an inflammatory nature, there is an increasing interest in the development of low molecular weight inhibitors that target this MIF enzymatic activity for use in treating inflammatory diseases [47].

Interference with the Cell Cycle

The p53 protein is the product of the TP53 tumor suppressor gene and acts as a transcription factor, regulating the expression of numerous genes, and plays a crucial role in controlling the cell cycle [48]. In normal cells, p53 remains bound to its Mdm2 inhibitor that tightly represses the p53 function, by inducing its degradation. When the incorrect base pairing occurs during the synthesis of DNA, p53 is phosphorylated and separated from Mdm2 and carries out its function, which is to stop the cell cycle and repair the DNA error. Once the repair is done, p53 is degraded and the cycle continues, leading to cell division [23].

MIF interacts with p53 in a manner dependent on the redox status and stabilizes the linkage between p53 and Mdm2, ensuring that p53 is not phosphorylated to become free and perform its function. This condition created by MIF leads to a decrease in the expression of p21 proteins, Bax and p53 itself. This negative regulation of p53 activity leads to the prevention of cell cycle arrest and inhibits cell death by apoptosis [49]. Inactivation of the p53 function can dramatically disrupt the DNA repair mechanisms, resulting in the accumulation of mutations and generating genomic instability that increases the risk of malignant transformation of the cell [50].

Suppression of the Immune Surveillance

MIF can suppress the antitumor immunity by several mechanisms. One of the most important is the inhibition of cytotoxic T lymphocyte (CTL) and natural killer (NK) cells, contributing to the escape of tumor cells of the immune surveillance [51]. Furthermore, MIF can activate the tumor cells to acquire the ability to inhibit the production of dendritic cells and to induce apoptosis of these cells. As the dendritic cells have anti-tumor action, this activity is impaired [52].

MIF can also inhibit the anti-tumor immunity by activating and increasing the production of myeloid-derived suppressor cells (MDSCs), which are highly immunosuppressive and which infiltrate the tumor [31, 32]. MDSCs use a variety of mechanisms to inhibit the function of T and NK cells, suppressing the anti-tumor immunity [53].

Moreover, MIF also promotes alternative macrophage differentiation, giving rise to tumor-associated macrophages (TAMs). As with the MDSCs, TAMs are abundant in the tumor environment and act together with MDSCs to develop immunosuppressive activity of NK and T cells [54], thus contributing to higher tumor aggressiveness [55].

Action as Growth Factor and Differentiation of Neuronal Cells

In addition to the versatile role of MIF in the immune system, it also acts as neurotrophins, a family of proteins belonging to a class of growth factors that act as regulators of survival, development, and neural cell plasticity. It has been demonstrated that MIF is widely expressed during embryonic development, particularly in the cells of the nervous system, but its role in neural development is still poorly understood [56]. However, it was found that MIF promotes the activation of proliferation and differentiation of neural stem/progenitor cells (NSPCs), which are cells with self-renewal capability and which can differentiate into multiple neuronal lineages during the development of the embryo and in the perinatal period [57]. These cells are essential for brain development and brain physiological functions. The niche where the NSPCs reside is a microenvironment that provides the conditions for the maintainability of the multipotent state of these cells, enabling their self-renewal. The components present in these niches are the source of extrinsic signals that instruct the NSPC self-renewal or differentiation and influence the decision of NSPC's fate into neuron or glia [57, 58].

MIF receptors, including CD44, CXCR2, CXCR4, and CD74, are expressed in NSPCs. This shows the potential regulatory effect of MIF on NSPCs, promoting the activation, the proliferation, and the differentiation of these neural stem/progenitor cells. It was shown that both Ki67-positive cells and neurosphere volumes were increased in a dose-dependent manner after treatment with MIF. It was also observed that, during MIF-induced NSPC differentiation, there was an increase in the activity of β-galactosidase, which responds to Wnt/β-catenin signaling, and that Wnt1 and β-catenin proteins were also up-regulated with MIF stimulation. On the other hand, doublecortin (DCX) and Tuj I, two neuronal markers, were clearly increased with MIF stimulation during NSPC differentiation. Moreover, the expression of DCX and Tuj 1 was inhibited significantly by IWR-1, the inhibitor of the Wnt/β-catenin pathway. It was also observed that the treatment with IWR-1 significantly inhibited the proliferative effect of MIF on NSPCs [57].

MIF and Cancer

Cancer is the uncontrolled proliferation of cells triggered by a suite of genetic and epigenetic events that disrupt the homeostasis of the human body. Standing out among them are the accumulation of mutations, especially of the tumor suppressor genes, conversion of proto-oncogenes to oncogenes, methylation DNA, and post-translational modifications, as well as the long-term persistent infection by certain infectious agents [14, 59]. The long-term chronic inflammation, together with disorders in immune response, has played a crucial role in process of carcinogenesis. The inflammatory milieu contributes in various stages of tumor development, including initiation, promotion, growth, and invasion, besides affecting the immune surveillance [60, 61]. Mediators such as cytokines, chemokines, PGE2, growth factors, transcription, and enzymes such as COX-2 and MAP act together to create a favorable environment for the tumor. These mediators engage in an extensive and dynamic crosstalk with cancer cells, triggering molecular events contributing to tumorigenesis [14, 61].

The association between chronic inflammation and cancer is well established, being widely accept that this condition can lead to the development and progression of tumors [27]. Studies performed since the discovery of MIF have increasingly strengthened its role in inflammation as well as in the innate and adaptive immune responses [23, 62]. In this context, because of its important role in regulation of the inflammatory and immune responses, MIF has been thought to be the link that connects inflammatory response to cancer [23].

MIF is a pro-inflammatory cytokine that is produced in the tumor environment and secreted by monocytes, macrophages, and tumor cells. Under inflammatory stimuli, cancer cells secrete growth factors and cytokines, which increase the potential for malignant transformation of cells, promote activation of tumor associated macrophages (TAMs), and interactions between stromal cells and of the tumor [63].

MIF participates in the regulation of both normal physiological and pathological conditions. Due to its pleiotropic action, MIF promotes inflammation, cell proliferation, and inhibition of cell death by apoptosis, and regulates migration, activation, differentiation and reprogramming of immune and non-immune cells. These functions are particularly important to upset homeostasis and create a microenvironment favorable to the development of cancer [64]. A remarkable overexpression of MIF was found in several types of humans cancer, including: squamous cell carcinoma of the esophagus [65], cervical cancer [66], breast [25], prostate [67], liver [68], lung [69], glioblastoma, neuroblastoma, colon and colorectal cancer [70], bladder [71], ovarian [51], endometrium [72], gastric and pancreatic [73], renal carcinomas [74], and lymphocytic leukemia B cells [75].

MIF interferes with multiple cellular signaling pathways through a complex networks of interactions. The production of MIF is activated through autocrine signaling emitted by the cancer cells, resulting in the stimulation of the production of cytokines, chemokines, and angiogenic factors, which lead to tumor growth, and the dissemination of tumor cells [16]. When binding to its receptor CD74, MIF leads to the recruitment of the hyaluronate receptor CD44, and this complex (CD74/CD44) that have been implicated in tumourigenic MIF signaling processes [76].

Currently, there is a general consensus that MIF promotes tumor growth by several mechanisms: it stimulates tumor cell proliferation by activating the MAPK/PI3K/Akt pathways, inhibits p53-dependent apoptosis, increases vascular endothelial growth factor (VEGF) production, and inhibits the antitumor immune response [27, 28, 51, 77]. Moreover, it modulates metastatic behavior of tumor cells and affects stromal tumor cells [78].

Angiogenesis is a complex process involving a series of cellular factors for the formation of new blood vessels [9]. Among the mediators involved in this process, the following stand out: the basic fibroblast growth factor (bFGF), VEGF, hypoxia inducible factor 1 (HIF-1), and angiopoetin, which are necessary for the formation of new blood vessels [9, 79]. Under conditions of stress and hypoxia, endothelial precursor cells secrete bFGF, VEGF, and other pro-angiogenic factors necessary for the formation of blood vessels [80]. The condition of hypoxia causes upregulation of HIF-1, which leads to increased expression of VEGF, bFGF, and angiopoetin. Furthermore, HIF-1 also induces the production of MIF, which, in turn, plays a key role in tumor angiogenesis [79]. It has been shown that MIF induces dose-dependent secretion of bFGF, VEGF, and IL-8 [81].

The overexpression of MIF also reduces the expression of e-cadherin [82], which is responsible for the formation of focal adhesion complex, maintaining the cells contact with each other and with the basal membrane. The decreasing of e-cadherin expression weakens the focal adhesion complex, leading to epithelial mesenchymal transition [23]. In the tumor environment are found high levels of MIF expression and other angiogenic factors, which result in an increase in expression of matrix metalloproteases (MMPs). These enzymes degrade the basement membrane, leading tumor cells to enter the bloodstream, and when they receive appropriate homing factors, they establish secondary tumors in different organs [23].

In cervical cancer a correlation was observed between the levels of MIF expression and histological grading of precursor lesions of cervical cancer of the invasive form, supporting the idea that MIF has effects in promoting tumor [24]. Also observed was a trend of increased MIF expression and of its receptor CD74 in normal cervical epithelium, cervical intraepithelial neoplasia (CIN), and squamous cell carcinoma (SCC). Besides, the expression MIF was correlated with microvessel density, inducing a dose-dependent increase in the VEGF secretion in cervical cancer cells. This suggests that over-expression of MIF and CD74 may be associated with

pathogenesis and angiogenesis in cervical cancer [66]. In prostate cancer, high expression of MIF and low expression of CD74 were detected [83]. Detected in cancers of lung and breast were high expression levels of MIF and a smaller and less uniform expression of CD74, mainly in the stromal compartment [84, 85]. In esophageal cancer and in the hepatocellular carcinoma (HCC), the over-expression of MIF has been correlated with a loss of cell differentiation and lymph node metastases. It is believed that by acting as an autocrine factor, MIF increases VEGF secretion, which promotes angiogenesis, tumor growth, and migration of tumor cells [65, 68].

Evidence indicates that MIF has a dual role in breast cancer. When it is found within the tumor cells, it may be indicative of a favorable prognosis. However, when found in an extracellular location in the tissue derived from the breast cancer, MIF may be pro-inflammatory and probably constitutes an unfavorable prognostic marker [63]. The presence of a significant increase in mean serum MIF levels has been reported in patients with breast cancer, compared to healthy women. In view of its autocrine and paracrine effects on cancer cells, MIF may contribute to shaping the microenvironment, leading to immunomodulation and angiogenesis [85].

The highly aggressive tumors attract cells of innate and adaptive immune responses to suppress anti-tumor immunity mediated by lymphocytes. Most of this immunosuppressive activity in patients in the final stage of melanoma is due to the action of a subpopulation of derived myeloid cells (MDSCs) of the monocytic subset, whose production is MIF-induced. These cells are producers of nitric oxide [86], prostaglandin, and express receptors for these lipid mediators [87], and are able to suppress both Ag-specific and nonspecific T cell proliferation [88]. An in vitro study on circulating MDSCs, isolated from melanoma patients in late-stage, showed that the immunosuppressive activity of these cells is MIF-dependent for suppression of antigen-independent T-cell activation and that MIF is required for maximum production of reactive oxygen species by these cells. Furthermore, inhibition of MIF resulted in functional reversal of T lymphocytes from the neutralization of the immunosuppressive activity of MDSCs, by action of an immunostimulatory dendritic cell (DC)-like phenotype that is, at least partly, due to reduced production of prostaglandin E2 (PGE2) by MDSC. These results indicate that MIF is directly involved in the induction of the immunosuppressive function of monocytic MDSCs in humans and that the therapeutic approach having MIF as the target may provide a novel means of inducing DC-mediated antitumor responses in late-stage melanoma patients [32].

The ability of NK and TCD8+ cells to eliminate malignant cells depends on the recognition of stress- or transformation-induced molecules that bind to receptor NK group 2D (NKG2D; 4) to activate NK and TCD8+ cells [89, 90]. Standing out among these molecules are the class I MHC components, MICA/B, and 1–4 ULBP, which are induced by DNA damage [89] and are found in cells infected by viruses and tumor cells [91]. When such molecules bind to the NKG2D receptor, this leads to the activation of the adaptor protein DAP10, which signals and initiates a perforin-mediated cytolytic response, which can lead to NK cell-mediated tumor clearance, without prior activation or Ag-specific tumor cell recognition [91]. It has been shown in studies in vitro and in vivo, that MIF contributes functionally to the immune escape of the ovarian carcinoma and malignant gliomas, through down-regulation of expression of NKG2D, which reduces the cytotoxic activity of NK and T-cells, suppressing the cellular immune response against the tumor cells [51, 90]. Additionally, it was reported that MIF increases the amount of MDSCs in the circulating blood of patients with a variety of tumors and acts by a variety of mechanisms to prevent the functions of NK and T-cells, suppressing the anti-tumor immunity [31]. It was further shown that in prostate cancer, the cancerous cells activated by MIF acquire the ability to kill dendritic cells by apoptosis and inhibits their production, thus avoiding the antitumor activity of these cells [52].

A study by Tanese et al. (2015) [92] showed that in cell lines derived from melanoma, MIF can reverse the IFN-γ role in immune surveillance against tumors, since IFN-γ increases the expression of the MIF receptor, the CD74 protein, in cell lines melanoma-derived. MIF interacts with its CD74 receptor on the surface of these cells, which results in signaling pathway activation of the P13K / AKT pathway and promotes the survival of tumor cells. IFN-γ promotes the phosphorylation of AKT Ser473, resulting in increased expression of protumorigenic factors such as IL-6, IL-8, and BCL2 in cell lines derived from human melanoma. The correlation between plasma levels of IFN-γ and MIF receptor expression in tumor cells has been found in samples from patients with melanoma. Furthermore, inhibition of MIF-CD74 interaction significantly suppressed tumor growth in the presence of IFN-γ in the mouse model [92].

A case-control study conducted by Wu et al. (2011) [93], involving Chinese women of the Shanxi province with and without cervical cancer, demonstrated a functional association between the single nucleotide polymorphism in the MIF gene (MIF-173) allele 173G/C and metastasis in the early stage of cervical cancer. These authors reported that women with the C variant of the MIF-173 allele had a significantly higher risk for cervical cancer, compared to carriers of the wild-type allele GG, and that the GC and CC genotypes behaved as risk factors for cervical cancer in the studied population. Individuals with the GC + CC genotype and C allele at the MIF-173G/C site were at a significantly higher risk of cervical cancer and lymphatic metastasis. The risk of lymph node metastases in the early stages of cervical cancer has increased by more than 1.6 times in patients with GC or CC genotype compared to those with the GG genotype. Also, a positive association was observed between high serum concentrations of MIF and

occurrence of early metastasis. In addition, patients with the CC genotype had higher MIF serum levels, indicating that this genotype increases the risk of lymphatic metastasis in women with early-stage cervical cancer. These results suggest that the MIF-173 polymorphism may be associated with increased risk of cervical cancer in women and that the quantification of MIF serum levels and genotyping of patients could be used as biomarkers of prognosis and for early treatment of the cervical cancer [93]. On the other hand, in a meta-analysis study, it was found that the polymorphism of the MIF gene -173G / C can increase the risk of cancer among Asians but not among Caucasians. The heterozygous mutational genotype CG could increase the risk of gastrointestinal cancer and hematological malignancy, while the homozygote genotype CC might increase susceptibility to gynecological cancer, as compared with the genotype wild type GG [19].

Several studies also show that MIF plays an important role in cancer development, in virtue of its ability to act in conjunction with other mediators to interfere in many cellular signaling pathways, creating a favorable environment for the tumor. Those conditions include the inflammation, cell proliferation, deregulation of the cell cycle, inhibition of apoptosis, suppression of immune surveillance against tumors, angiogenesis, and metastasis [23, 51].

In conclusion, MIF is a protein with pleiotropic action produced by virtually all cell types, presenting a variety of biological effects on the human body, participating in a complex chain of events that, together, favors the process of carcinogenesis. Experimental and clinical studies suggest that MIF could have a multifunctional role in the development of several human cancer types. Evidence shows that MIF exercises autocrine and paracrine effects on cancer cells, promoting the proliferation and migration of these cells, and inhibits apoptosis and autophagy. It also contributes to shaping a tumor microenvironment by acting on immune and non-immune cells, leading to immunomodulation. Thus, the necessary conditions are created for proliferation of cancer cells, resulting in growth, promotion, and tumor invasion. Additionally, MIF acts systemically to influence a complex network of cellular signaling pathways, leading to an imbalance of homeostasis and causing metabolic disorders such as metabolic syndrome and its potential negative implications on the immune system, which contribute to tumor growth and the development of metastases.

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