

Medicine

Is Macrophage Migration Inhibitory Factor a Link between Inflammation and Tumor?

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Macrophage migration inhibitory factor (MIF) is a classic pro-inflammatory factor that helps control both innate and adaptive immune responses. The expression of MIF is much higher in many tumor tissues, which helps the tumor grow, spread, make new blood vessels, and create an immune microenvironment that helps the tumor. Due to the important role MIF plays in the development and growth of tumors, it is being looked at as a possible way to treat tumors. This review discusses what MIF is, where it is found, how it sends signals, what it does in inflammation and tumors, and how drugs that target MIF are being made.

Keywords: Macrophage Migration Inhibitory Factor; Inflammation; Tumor; Microenvironment; Therapeutic Target

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ONE of the most prevalent and intricate pathological processes in human diseases is inflammation. Rudolf Virchow first suggested that there was a connection between inflammation and cancer in 1863 (1, 2). Accordingly, microbial infections trigger an inflammatory response that accounts for 20% of human malignancies (3, 4). Chronic inflammation can dramatically raise the risk of cancer. Inflammation is a key factor in carcinogenesis. Not only does inflammation contribute to carcinogenesis, but it also speeds up the development of tumors. Typically, a substantial number of inflammatory cells infiltrate the tumor microenvironment, which promotes the formation of malignant tumors by secreting growth factors, pro-inflammatory cytokines, and chemokines, among other substances (5). Inflammation-related signaling pathways like NF- κ B and STAT3 signaling were also noticeably activated in clinical tumor samples (6, 7).

Macrophage migration inhibitory factor (MIF) is a multi-functional protein with the ability to control the production of other pro-inflammatory factors as well as operate as a cytokine to play a pro-inflammatory role (8). D-dopachrome tautomerase, phenylpyruvate tautomerase, and thiol protein oxidoreductase activity, which can catalyze a variety of metabolic reactions, are three of MIF's key characteristics (9). MIF is a crucial regulator of the inflammatory response process and the primary upstream mediator of the innate immune response mechanism (10). Studies have discovered that solid tumor tissues like breast cancer, prostate cancer, and pancreatic cancer produce MIF at considerably higher levels than normal tissues, and that this difference is directly correlated with the potential of the tumor to metastasize and invade (11). Through inflammatory reactions, immunological responses, and the tumor microenvironment, MIF is directly implicated in the regulation of tumor cells while also playing an

indirect role in the emergence of tumor-related illnesses.

As the biological role of MIF has been thoroughly studied, it is gradually becoming seen as a key target for the treatment of immune-related illnesses, inflammation, and even the creation of anti-tumor medications (12). For the development of anti-inflammatory and anti-tumor drugs targeting MIF, a thorough understanding of the structural properties and signal regulation of MIF, as well as the clarification of the regulatory role and mechanism of MIF in the process of inflammation and tumor development, are of utmost importance. This review discusses the properties and distribution properties of MIF, signal transduction pathways associated with MIF, the regulation of MIF in the course of inflammation and tumor growth, and the creation of MIF-targeting medications.

The Characteristics and Distribution of MIF

The Origin and Characteristics of MIF

Bloom et al. found for the first time in 1966 that activated T cells could create a cytokine that not only promoted the inflammatory response but also inhibited the random migration and adherence of monocytes/macrophages, which they termed MIF (13). The human MIF gene has three exons and two introns and is located at 21q22.3. It has a relative molecular mass of roughly 12.5 kDa. According to X-ray crystallographic photos, the human recombinant protein MIF has an irregular structure and exists as a homotrimer, with the monomer constituted of two antiparallel helices and a sheet formed by four chains (14).

MIF, in contrast to other cytokines, is a multifunctional protein. MIF is a pleiotropic cytokine as well as an endocrine factor expressed and produced by endocrine organs such as the brain, pituitary, and adrenal glands (15). MIF has at least three different enzymatic activities: D-dopachrome tautomerase, hydroxyphenylpyruvate tautomerase, and oxidoreductase (16). The amino-terminal proline (Pro) residue of MIF plays a key role in the catalytic activity of tautomerase, and other important residues are Lys-32, Ile-64, Tyr-95, and Asn-97, all of which have been determined to be generally conserved throughout evolution (17). MIF's oxidoreductase activity is dependent on the CALC amino acid sequence (Cys57-Ala-Leu-Cys60), and an intramolecular disulfide bond can form between Cys57 and Cys60 (18). MIF oxidoreductase activity is critical for maintaining intracellular redox equilibrium, resisting oxidative stress, preventing cell apoptosis, and activating macrophages (19). Furthermore, MIF is the sole immune factor that inhibits glucocorticoids (20).

MIF Distribution Characteristics

MIF can be made by T lymphocytes, monocytes, macrophages, and cells in the brain, lungs, liver, kidneys, genitourinary system (21). However, MIF is mostly made up of anterior pituitary cells, peripheral monocytes/macrophages, and activated cells (22). MIF is a constitutive expression factor, which is synthesized in advance and stored in the cytoplasm and can be directly secreted when stimulated without re-synthesis (23). MIF can be made by both immune cells and non-immune cells. However, MIF does not have an N-terminal leader signal peptide sequence that is transported to the endoplasmic reticulum. This means that MIF's

secretion process is not the same as most other proteins. Merk et al. found that the extracellular release of MIF needs to interact with the intracellular Golgi complex-related protein p115 (24). Flieger et al. found that glibenclamide and probenecid can reduce the extracellular release of MIF (25). The ABCA1 transporter, which is a member of the ABC transporter family, is involved in the process of MIF secretion (26). MIF can also regulate itself through an autocrine loop through JAB1 (27, 28). Recent evidence indicated that autophagic modulation of mitochondrial ROS is essential for the regulation of macrophage MIF secretion (29, 30).

Regulatory Function and Signal Transduction Pathway of MIF

Regulatory Function of MIF

MIF primarily interacts with membrane receptors of the CXC family (such as CXCR2, CXCR4, CXCR7, and CXCR12), CD74, and CD44, activating downstream signaling cascades and performing biological tasks (31-33). Leng et al. (17) discovered that the membrane protein CD74 is a high-affinity receptor for MIF, and that MIF can regulate CD74 activity, resulting in homeostasis abnormalities such inflammation, malignancies, and autoimmune illnesses (34). MIF not only activates the MAPK signaling pathway via CD74, but it also continually activates the ERK signaling pathway (35). Rajasekaran et al. discovered that combining MIF with the chemokines CXCR2 and CXCR4 attracted leukocytes and accelerated atherosclerosis (31). Further research has revealed that these membrane receptors typically bind to MIF as complexes (such as CXCR4/CD74, CXCR2/CD74, and CD74/CD44) to regulate cell functions, such as the binding of MIF to CD74/CD44 complexes to activate Syk, Akt, NF- κ B, and other signals that regulate the immune response (36).

MIF has biological roles not just extracellularly, but also in the cytoplasm, and intracellular MIF modulates cell functions via protein-protein interactions. MIF interacts with the serine protease HTRA1, inhibits the hydrolysis activity of the HTRA1 protein, and influences cell growth and differentiation (37). MIF binds to the thioredoxin TXNIP, on the one hand, up-regulates NF- κ B, and on the other hand, suppresses TXNIP's tumor suppressor activity, hence promoting tumorigenesis (38). Shen et al. discovered that MIF interacts with the apoptosis-related protein BNIP1 and contributes in cell apoptosis (39).

MIF Signal Transduction Pathway

Most of the signaling molecules that are related to MIF are JAB1/JNK, ERK, PI3K/Akt, and p53. Both MIF and JAB1 are regulated by each other. MIF keeps JNK and AP-1 from getting phosphorylated by JAB1 (40). This changes the cell cycle, controls cell growth, division, and death, and JAB1 can also stop the production of MIF. MIF indirectly upregulates ERK1/2 signaling molecules through the receptor CD74/CD44 complex. It also increases the expression of a number of molecules that come after it, such as PLA2, COX-2, p53, MSK1, and RSK1. The up-regulation of COX-2 is a key part of the pro-inflammatory response (41, 42). At the same time, COX-2 can stop the buildup of p53 in cells and stop cell death, which is

a key part of the development of autoimmune diseases and cancer (43, 44). Matrix metalloproteinases are also controlled by MIF, which is done through ERK signaling (45). MIF turns on the ERK/MAPK signaling pathway to make MMP9 come out (46).

MIF's ability to stop apoptosis and help new blood vessels grow is closely linked to the activation of PI3K/Akt signaling molecules. Akt can phosphorylate BAD and help Bcl-2 and Bcl-xL stop cells from dying by apoptosis (47, 48). In glioma, angiogenic mimicry is also controlled by the MIF/Akt signaling pathway (49, 50). Through PI3K signaling molecules, MIF encourages the release of things like VCAM-1 and ICAM-1, and it also helps control how blood vessels work (51). The interaction between MIF's cysteine 81 and p53's cysteine 81 controls not only how p53 is controlled, but also how it is broken down (52). From the above studies, it is clear that the relationship between MIF and these signaling pathways is not a separate one, but rather a network of controls. Also, the way MIF is controlled on these signaling pathways cannot be generalized, so more further studies are needed on MIF signaling molecules and signaling pathways.

MIF is Involved in Inflammation and Tumor Regulation

Pro-Inflammatory Function of MIF

David et al. discovered that MIF was involved in delayed-type hypersensitivity (53). They also discovered that the expression of MIF was positively linked with the severity of the allergic reaction, suggesting that MIF is a pro-inflammatory factor. A number of inflammation-related disorders, including septic shock (54), glomerulonephritis (55), chronic enteritis (56), and rheumatoid arthritis (57), have been linked to MIF. When TNF is upregulated in ankylosing spondylitis, MIF causes osteoblast activity to increase, accelerating the progression of the disease (58). Chronic nephritis patients have considerably higher levels of MIF expression in their blood, which, in turn, activates the ERK/MAPK, JAB1/AP-1, and NF- κ B signaling pathways, triggering a series of pro-inflammatory cascade reactions, and hastening the progression of chronic nephritis (55). However, Stoppe et al. discovered that following heart surgery, the amount of MIF in serum increased, which decreased the consequences of acute nephritis (59). The occurrence of injury suggests that MIF may also have a protective impact on acute kidney injury, albeit the precise mechanism is still unknown. MIF has a chemokine-like function, participates in the production of other pro-inflammatory factors, such as TNF- α , IFN- γ , IL-1, IL-6, IL-8, and IL-12, etc., and specifically neutralizes the anti-inflammatory response caused by glucocorticoids. These pro-inflammatory factors control inflammatory responses such as autoimmune diseases and infections (60). By influencing the makeup of the gut microbiota, MIF is also involved in the onset and progression of inflammation associated to the gut (61).

Tumor-Promoting Effect of MIF

MIF is a well-known pro-inflammatory factor that has a significant impact on immune function and inflammation. The expression of MIF is much higher in common solid tumors than in

healthy tissues, including liver cancer, prostate cancer, colon cancer, bladder cancer, and lung adenocarcinoma (62). MIF takes role in the preservation of tumor cells' unrestricted angiogenesis, anti-apoptosis, and immune evasion. By creating a microenvironment that supports tumor growth, MIF, a particular protein that promotes tumor growth, not only directly contributes to the regulation of tumors but also indirectly hastens the onset of tumor-related disorders.

MIF Promotes Tumor Cell Proliferation

As a factor that makes tumors grow, MIF helps control many of the biological features of tumor cells. Takahashi et al. showed that slowing the expression of endogenous MIF slowed the growth of tumor cells (63). Knocking down MIF in liver cancer cells like PLC and HepG2 could stop tumor cells from multiplying (64). Tumor suppressors can start the process of apoptosis in a cell, which is the key to keeping the balance between cell death and growth. p53 does not work right in 50% of human tumors (65). MIF can stop cells from aging and dying by stopping the phosphorylation of p53 and reducing the transcriptional activity of p21, Mdm2, and cyclin G1 (66, 67). When MIF was taken away from cervical cancer cells, the expressions of pro-apoptotic proteins like Bax, caspase-3, and cleaved-PARP went up, while the expressions of anti-apoptotic proteins like Bcl-2 and pAkt went down. This showed that MIF stopped cervical cancer cells from multiplying (68). MIF slows down apoptosis, and miR-451 speeds up apoptosis in osteosarcoma cells by downregulating MIF (69), while miR-146a speeds up apoptosis in lung cancer cells by stopping MIF from being expressed (70). Studies like the ones listed above have shown that MIF can stop tumor cells from dying and make them grow faster.

MIF Promotes Tumor Angiogenesis

When the tumor reaches a particular size, it will develop its own circulatory system to supply it with an abundance of nutrients and oxygen. If there are no new blood vessels supplying nutrition to tumor cells, the average diameter of tumor tissue is less than 3 mm. It is evident that the development of a new blood artery is crucial for tumor growth and spread (71). The expression level of MIF in patients with pulmonary arteries was positively correlated with Ang1, VEGF, PDGF-BB, FGF-basic, PLGF and other vascular growth factors, which promoted the formation of new blood vessels (72). Knocking down MIF could significantly reduce the expression of VEGF and PECAM, and inhibit angiogenesis (73). Jia et al. discovered that miR-1228 through targeted inhibition of MIF inhibits tumor angiogenesis (74). These findings indicate that MIF participates in tumor angiogenesis and promotes tumor development. In addition, MIF is a potent pro-angiogenic growth factor capable of directly promoting the proliferation of endothelial cells and the construction of the vascular system (75).

MIF Induces and Maintains the Characteristics of the Tumor Microenvironment

The microenvironment of a tumor consists of tumor cells, diverse stromal cells, tissue fluid, and invading inflammatory cells. These characteristics are important for tumor cell proliferation,

invasion, metastasis, and neovascularization. Inflammatory cells, particularly tumor-associated macrophages (TAM), are an essential component of the tumor microenvironment and play a crucial role in the inflammation-tumor axis. MIF is able to control the polarity of TAMs. In malignancies, macrophages typically develop into tumor-promoting M2-type TAMs, which promote tumor cell proliferation and spread and block anti-tumor immune responses (76). MIF is an immune regulator in the tumor microenvironment, causing the creation of an immune milieu that suppresses tumor growth. In advanced melanoma, MIF promotes tumor growth and metastasis by inducing the differentiation of suppressive immune cells (77). Tumor cells secrete MIF factors into the microenvironment, thereby recruiting a large number of S100A8-positive bone marrow cells, thereby forming an inhibitory immune microenvironment that is conducive to immune escape of tumor cells (78). By changing the activity of immune cells, these findings imply that MIF can weaken the body's immunological response and encourage the formation of malignancies.

One of the primary characteristics of the tumor microenvironment is hypoxia. Hypoxia can cause tumor cells to express hypoxia inducible factor (HIF). HIF binds to hypoxia response elements (HREs) and activates LOX, CTG, and VEGF, among other targets (79). Hahne et al. discovered that MIF is the target gene of HIF-1 and HIF-2, that HIF promotes inflammation and tumor formation by upregulating MIF, and that it participates in angiogenesis by upregulating MIF (80). The regulation between MIF and HIF-1 is, in reality, reciprocal. Breast cancer cell lines MCF-7 and MDA-MB-231 express large levels of MIF, and that this MIF contributes to the maintenance of HIF-1 (81). Activated HIF-1 increases the expression of MIF, so generating a positive feedback regulation between MIF and HIF-1, thereby enhancing the adaptability of tumor cells to hypoxic environments and speeding tumor growth.

Studies have demonstrated that MIF promotes tumor cell invasion and metastasis by upregulating pro-inflammatory factors, metal matrix proteases, and extracellular matrix degradation enzymes, which is conducive to tumor cell metastasis. The expression level of MIF in metastatic melanoma was significantly higher than that in non-metastatic melanoma (82). Liver endothelial cells secrete MIF into the surrounding environment, thereby promoting the expression of MIF in rectal cancer cell lines (83). Transfer of growth after knocking down MIF in oral squamous cell carcinoma, the expression of the epithelial-mesenchymal transition marker Twist1 and matrix metalloproteinase MMP9 reduced, showing that the high expression of MIF in tumor cells promotes tumor cell invasion and metastasis (84).

Targeting MIF Therapeutic Strategies

MIF possesses pleiotropic physiological roles and catalytic activity and is involved in the occurrence and progression of numerous inflammatory, immunological, and neoplastic illnesses. This makes it an important target for the development of anti-inflammatory and anti-tumor medications.

Reduce MIF Enzyme Activity

Currently, the majority of medications that target MIF are small

molecule inhibitors that block its enzyme function. These inhibitors are typically found using computer aided drug design (CADD) and virtual screening (VS) technology. Small molecule inhibitors come in at least 11 different varieties, and their main modes of action are to: bind to the enzyme's active site, causing it to lose enzyme activity; inhibit tautomerization; modify the valence of molecules; inhibit the formation of trimers (with tautomerase activity); and induce trimer dissociation (85).

MIF enzyme activity can be inhibited by the small molecule inhibitor ISO-1, which also reduces the proliferation, invasion, and metastasis of a number of tumor cell lines, including A549, DU145, LN229, and HS683. ISO-1 also has a good anti-tumor effect in vivo tumor model (86). Although ISO-1 has been used extensively in preclinical studies, it has some flaws with intraperitoneal delivery and enzyme kinetics. Then, ISO-66 and ISO-66 based on ISO-1 were optimized, which is less cytotoxic and more stable than ISO-1 (87). 4-Indole-6-phenylpiperidine (4-IPP) is an inhibitor of MIF/D-DT dual targets (88). Ebselen, ibudilast (AV411, AV1013), and p425 are the three main allosteric inhibitors of MIF that have been reported to date (89). They can drastically lower MIF activity, p425 can also prevent MIF from binding to CD74, limit the activation of MIF's downstream signaling, and more research is still needed to determine the anticancer effects of these inhibitors. Recently, it was found that substances like vitamin E and the isocoumarin molecule SCD-19 can target MIF and limit its biological activity (90). Drugs aimed at MIF have also been created by some pharmaceutical companies. For instance, MIF inhibitors CPSI-2705 and CPSI-1306 were studied by Cytokine Pharma Sciences (91) while AVP-13546 by Avanir Pharmaceuticals was found to be a MIF inhibitor (92).

Reduce the Amount of MIF Protein

Heat shock protein 90 (HSP90) in tumor cells can keep MIF stable, and the HSP90 inhibitor 17AAG can speed up the breakdown of MIF and stop the growth of tumor cells (93). Blocking HER2 can also stop HSP90 from keeping MIF stable (94), which suggests that HER2 inhibitors can also speed up the breakdown of MIF and reduce the amount of MIF inside cells. It can be seen that destroying the stability of MIF to make it break down faster or stopping the transcription of MIF to lower the amount of MIF in cells is also a way to try to find drugs that target MIF. For example, NADPH oxidase 4 can increase the amount of MIF mRNA and protein (95). So, research that focuses on NADPH oxidase 4 may be able to find new inhibitors for the expression of MIF, which could give researchers who are looking for drugs that target MIF new ideas.

MIF Antibody

Due to their short half-life, high cost, and probable immunogenicity, the development and application of antibodies are severely limited. With the effective application of an increasing number of monoclonal antibodies (such as rituximab, trastuzumab, and aletuzumab), antibody drugs are gaining popularity among the general public. BaxG03, BaxB01, and BaxM159, which suppress MAPK/ERK1/2 activity by targeting MIF, lower the proliferation and invasion capacity of prostate cancer cell PC3, and considerably inhibit tumor growth, have also emerged succes-

sively (96). In addition, phase I clinical trials of MIF monoclonal antibodies have been launched (97); in the CT26 colon cancer model, anti-MIF neutralizing antibodies also have an excellent tumor suppressive effect (98).

Although progress has been made in the study of pharmacologically target on MIF, these inhibitors still have a number of drawbacks, including low activity, low effectiveness, low selectivity, and numerous side events. Although a number of MIF inhibitors have been described and have demonstrated promising anticancer effects in vitro, no MIF-targeting medicines are currently on the market. Therefore, it is of the utmost importance to discover innovative medication development strategies that target MIF. Peptide medicines that target MIF are one of the new therapeutic approaches. Peptides possess a low molecular weight, a simple structure, and little or no immunogenicity. Based on this screening of peptide medicines that bind to MIF selectively, inducing MIF inactivation or boosting its degradation is an effective MIF targeting method. siRNA medicines that target MIF are a further developing method. siRNA can target a specific gene and has the benefits of high efficiency, durability, and high specificity. Transient transfection of MIF siRNA reduced the proliferation and metastasis of oral squamous cell carcinoma (99). Additionally, looking for antibody-drug conjugates (ADCs) targeting MIF (100), was found

to reduce the proliferation and metastasis of oral squamous cell carcinoma. Small molecule medications are connected to directly target the tumor, hence decreasing chemotherapy's harmful effects (101).

Conclusion

Studies have revealed that MIF regulates immune and inflammatory responses, which in turn affect tumor cell growth, invasion and metastasis, angiogenesis, and the induction of tumor suppression. As a result, MIF not only directly affects tumor cell division and malignant transformation brought on by oncogenes. MIF is one of the key targets for the therapy of tumor as a result. MIF is a crucial multifunctional protein that plays a crucial role in the inflammation-tumor axis and serves a number of enzymatic functions in addition to acting as a cytokine. Researchers' knowledge of MIF-related disorders will increase as a result of the in-depth investigation of the MIF protein and the ongoing clarification of its function. It will also be advantageous for the creation of MIF-targeting medications. The study of MIF's role currently has certain practical applications, such as it may be utilized as a diagnostic marker for certain disorders. Further research is required since MIF's pathophysiological function, enzyme activity, signal transduction mechanism, and associated biological functions are still not fully understood. ■

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