

Review

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Inflammation and cancer: macrophage migration inhibitory factor (MIF)—the potential missing link

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Summary

Macrophage migration inhibitory factor (MIF) was the original cytokine, described almost 50 years ago and has since been revealed to be an important player in pro-inflammatory diseases. Recent work using MIF mouse models has revealed new roles for MIF. In this

review, we present an increasing body of evidence implicating the key pro-inflammatory cytokine MIF in specific biological activities related directly to cancer growth or contributing towards a microenvironment favouring cancer progression.

Introduction

Historically, the association between inflammation and cancer has been well recognized. In the 1970s, serum derived from BCG-infected endotoxin-treated mice was shown to induce significant necrosis in sarcoma tumour.¹ This active circulating cytokine was identified and consequently called tumour necrosis factor (TNF). More recently, a number of chronic inflammatory diseases have been shown to be associated with a variety of cancers (Table 1). With inflammation known to contribute to cancer development and progression, investigating the association between these two processes has never been more important. Macrophage migration inhibitory factor (MIF) displays a number of functions which provide a direct link between the processes of inflammation and tumour growth.

MIF was one of the first cytokines to be described almost 50 years ago and extensive studies since have revealed its central role in innate and adaptive

immunity. More recently, the ability of this cytokine to support tumour progression has become clear and has revealed MIF as a potential target for anti-cancer therapies.

MIF was originally identified as a T-cell-derived factor responsible for the inhibition of macrophage migration in experiments designed to characterize delayed-type hypersensitivity.^{2,3} The molecule is expressed by a variety of cells including eosinophils,⁴ epithelial cells,⁵ endothelial cells,⁶ lymphocytes⁷ and macrophage⁸ and so, predictably, displays a wide range of activities. *In vivo* stimulation with endotoxin promotes secretion of MIF from pools of stored protein within the cell allowing immediate amplification of the inflammatory response. Studies showing that MIF-specific blocking antibodies could attenuate endotoxic shock confirmed the critical role that MIF plays in innate immunity.⁹

The crystal structure of MIF revealed the active form to be a 37.5 kDa homotrimer with novel protein folds that defined a new structural

Table 1 Chronic inflammatory conditions associated with enhanced risk for specific cancers

| Inflammatory condition | Corresponding cancer |
|--|--|
| Barrett's oesophagus | Esophageal cancer ⁴⁸ |
| <i>Helicobacter pylori</i> infection | Gastric cancer ⁴⁹ |
| Inflammatory bowel disease | Bowel cancer ⁵⁰ |
| Hepatitis B or C | Hepatocellular carcinoma ⁵¹ |
| Obesity-related inflammation | Liver cancer ⁵² |
| Tobacco-particulate induced inflammation | Lung cancer ⁵³ |
| Coeliac disease | Lymphoma ⁵⁴ |
| Rheumatoid arthritis | Lymphoma ⁵⁵ |
| Schistosomiasis | Bladder cancer ⁵⁶ |
| Osteomyelitis | Sarcoma ⁵⁷ |

superfamily.^{10,11} In addition to its distinctive structure, MIF possesses a unique enzymatic activity revealed through its structural homology to several bacterial enzymes. This tautomerase activity mediated by an N-terminal proline residue, allows MIF to catalyse the conversion of non-physiological substrates D-dopachrome or L-dopachrome methyl esters to their indole derivatives. As yet, no human physiological substrates for MIF tautomerase have been identified.

The discovery that MIF was secreted from corticotrophic pituitary cells led to its classification as a hormone as well as a cytokine. Its release coincides with, and is induced by adrenocorticotrophic hormone and its ability to override the anti-inflammatory effects of this hormone suggested an inbuilt regulatory mechanism.⁹ This ability to promote inflammation while hindering the anti-inflammatory effects of glucocorticoids was implicated in the pathogenesis of acute respiratory distress syndrome (ARDS).¹² Direct association between MIF expression levels and degrees of disease pathogenesis in a number of inflammatory diseases was revealed through analysis of genetic variation within the MIF gene.^{13–15} Allelic variation within a repeat region found upstream of the MIF promoter, determines efficiency of expression of the protein. Individuals carrying five copies of the CATT repeat element were found to display lower MIF levels, with those possessing increasing numbers of repeats (6, 7 or 8) having a corresponding increase in expression. In cystic fibrosis patients, this increase in MIF production associated with carrying the 6 and 7 repeat variants was associated with enhanced end-organ injury. Rheumatoid arthritis patients carrying the 6 and 7 repeat variants had both higher basal levels of MIF and higher levels following stimulation with

forskolin or serum. The higher levels of MIF associated with this particular variant also correlated with progressive disease.¹⁶ In relation to malignant diseases, individuals carrying the seven-repeat allele were also found to have an increased incidence of prostate cancer.¹⁷ MIF biological activity has also been implicated in the pathogenesis of atherosclerosis and abdominal aortic aneurysm.¹⁸ In the context of atherosclerosis, MIF has also been identified as a non-cognate receptor of CXCR2 and CXCR4 and has functional chemokine activity in evolving atherosclerosis mediating monocyte arrest and the formation of plaques.¹⁹ Additionally, as part of this disease process MIF can induce the CXCR ligand, Interleukin (IL)-8 and regulators of macrophage infiltration ICAM-1 and CD44, confirming its relevance in this disease.²⁰

Mounting evidence suggests that inflammation is closely associated with many types of cancer.²¹ Inflammatory pathways designed to defend against infection and injury can promote an environment which favours tumour growth and metastasis. Chronic inflammatory conditions and infections have been directly linked to specific cancers, see Table 1. Supporting this observation, treatment with non-steroidal anti-inflammatory drugs has been shown to reduce the risk of developing colon cancer.²² Consequently, there is heightened interest both within academia and industry, to define key regulatory events within the inflammatory process which predispose individuals to enhanced cancer risk. This would provide the rationale for significant investment in these high-value therapeutic targets for drug development.

MIF and cancer

MIF's unique biological activities have the potential to contribute to an *in vivo* microenvironment favouring tumour growth and invasiveness. These functional activities include: tumour suppressor downregulation, COX-2 and PGE2 upregulation, potent induction of angiogenesis and enhanced tumour growth, proliferation and invasiveness (summarized in Table 2).

MIF and the tumour suppressor p53

MIF demonstrates a direct link between inflammation and tumourigenesis. As well as its established role in inflammation, MIF directly promotes tumourigenesis by inhibiting p53 accumulation. P53 is a classic tumour suppressor gene that can promote cell cycle arrest and apoptosis in response to DNA damage. Absence or downregulation of p53

Table 2 MIF biological activities which favour tumour pathogenesis

| MIF functional activities | Role in tumourigenesis |
|--|---|
| P53 inhibition | Accumulation of mutation Inhibition of apoptosis Proliferation of cells |
| Sustained ERK activation | Promotes invasion Inhibits cell death |
| COX-2/PGE-2 induction | Tumour Growth Viability Metastasis |
| Endothelial cell proliferation and differentiation | Promotes angiogenesis |

interferes with this important checkpoint for maintaining genetic stability and allows cell survival and proliferation despite the potential accumulation of mutations. Functional screens carried out by Hudson *et al.*²³ to identify cDNAs capable of negatively regulating p53 identified MIF. Over-expression of MIF down regulated p53 levels and suppressed nuclear localization, thereby prohibiting its transcriptional activity. Most importantly, MIF-suppressed p53-dependent senescence in primary mouse embryonic fibroblasts (MEFs) and inhibited apoptosis induced by serum starvation. Furthermore, in a separate study, a role for MIF in suppression of activation-induced cell death (AICD) was identified using MIF null mice.²⁴ Lipopolysaccharide administration produced increased macrophage AICD and an associated decrease in inflammatory cytokines in MIF null mice compared to wild-type mice. This again points to the key role MIF plays in amplifying inflammation, as well as promoting cell survival.

An important event in many cancer cells is the activation of endogenous oncogenes such as the prototypic oncogene Ras. Ras is a GTP-ase signalling molecule capable of promoting cell proliferation and malignancy. MIF-deficient cells were found to be resistant to p53-associated Ras oncogenic transformation which is mediated downstream through Rb and E2F. Transformation induced by Ras was restored upon deletion of p53.^{25,26}

MIF receptor signalling and tumour pathogenesis

MIF protein is found to be over-expressed in a number of cancers and expression levels have been found to correlate with disease severity and invasiveness. For example, in a mouse model of

intestinal cancer, MIF expression was found to be increased in tumour tissue relative to normal intestine. In addition, MIF added exogenously to a human colon adenocarcinoma cell line promoted anchorage-independent growth of the cells and inhibited cell death.²⁷ As well as its interactions with tumour suppressors, MIF promotes cellular proliferation through activation of members of the MAPK family. MIF signalling through CD74 promotes sustained ERK activation. The importance of this activity is clear when you consider that this is the main outcome of mutations in Ras which occur in a third of human tumours.²⁸ MIF stimulates phosphorylation of p42/p44 MAPK through PKA. This results in downstream activation of cPLA2 and release of the prostaglandin precursor arachadonic acid, a potential substrate for COX-2 now known to be induced as an important element of p53 inhibition by MIF. Sustained ERK activation is also observed in the PC12 model of neuronal differentiation, again suggesting a role for MIF in cell cycle progression.²⁹

While CD74 mediates MIF binding, a co-receptor, CD44, is required for ERK 1 and 2 phosphorylation.^{30,31} Blocking of MIF or MIF signalling, by blocking CD74 attenuates prostate cancer invasiveness.³² Conversely, activation of CD44 promotes breast cancer cell invasion.³³ CD44+ breast cancer cells with low or undetectable CD24 have been found to be more tumourigenic and have a characteristic 'invasiveness gene signature'.³⁴ Studies have also shown that CD44-positive prostate cancer and breast cancer cell lines demonstrate rapid adhesion to bone marrow endothelial cells which can be blocked by neutralizing CD44 antibody.³⁵ B lymphocytes that accumulate in chronic lymphocytic leukaemia have been found to have high expression of CD74 and stimulation of these cells with MIF induces anti-apoptotic Bcl-2 and promotes survival through an IL-8-dependent mechanism.³⁶ Blocking MIF signalling in this context decreases using anti-CD74 antibodies decreases cell survival.

MIF, hypoxia and angiogenesis

Hypoxia is very often associated with the tumour micro-environment. These hypoxic conditions in turn have been found to induce in tumours expression of specific patterns of genes which confer a survival advantage on cancer cells allowing tumour growth and spread in this environment. The master transcription factor HIF1 α (hypoxia inducible factor) binds to HREs (hypoxia response elements) in the promoter of its target genes to activate their expression.³⁷ These targets include pro-invasive and pro-angiogenic genes such as

LOX, CTG³⁸ and Vascular endothelial growth factor (VEGF).^{39,40} Simultaneously, HIF1 α negatively regulates anti-angiogenic targets such as thrombospondin.⁴¹ MIF is a direct transcriptional target of HIF-1 α and, more importantly, loss of MIF results in inefficient HIF-1 α stabilization induced by hypoxia.⁴² MIF expression has been found to be up-regulated during hypoxia, with a HRE found in the 5'Untranslated Region of the gene.^{43,44} MIF also supports tumour growth in a hypoxic environment through significantly enhancing angiogenesis. Through the activation of MAP kinases MIF enhances the differentiation of endothelial cells to blood vessels.^{45,46} In human breast cancer cells, MIF over-expression correlates with IL-8 and VEGF expression associated with angiogenesis.⁴⁷

MIF, enzymatic activity and tumour progression

A unique functional characteristic of MIF, which sets it apart from other cytokines is its enzymatic activity.⁵⁸ The precise role of this novel tautomerase enzymatic activity has not been fully defined. In relation to cancer pathogenesis, investigators have sought to define this enzymatic activity by both utilizing catalytically inactive recombinant proteins *in vitro* and in animal models by using a transgenic mouse expressing enzymatically inactive MIF.⁵⁹ The P1G mouse expresses a mutated MIF where a terminal proline has been replaced by a glycine resulting in specific loss of this enzymatic activity. While binding of MIF to CD74 and JAB1 was not significantly reduced, the mutation eliminated MIF enzymatic activity and intriguingly impaired specific MIF biological activity. With regard to cancer animal models, chemically induced skin tumours are less effectively induced in P1G mutant mice. This work suggests that apart from a potential role for the enzymatic activity, the tautomerase site is also required for important protein-protein interactions.

Small molecular weight inhibitors of MIF tautomerase activity have also been used to dissect out the importance of this unique activity in cancer pathogenesis. ISO-1 is one such inhibitor designed to fit into the catalytic site of MIF.⁶⁰ Using colorectal cancer as a model where serum concentration of MIF have been shown to correlate with increased risk of metastasis to the liver, *in vivo* treatment of colon carcinoma-bearing mice with ISO-1 results in decreased tumour volume, reduced angiogenesis and less liver metastasis.⁶¹ ISO-1 has also been shown to restore dexamethasone sensitivity in glioma cells which inhibits MIF-induced promotion

of migration and invasion of the cells via MAP kinases. Both enzyme kinetic studies and *in vivo* toxicity studies suggest a limited role for ISO-1 in human studies. However, our expanding knowledge of this novel enzymatic activity in human disease provides the rationale for the further development of more refined small molecular weight enzymatic inhibitors targeting specifically this novel activity.

It is our conjecture that individuals who are genetically predisposed to exhibit chronic injurious inflammation are at enhanced risk of cancer progression. Our expanding knowledge of MIF biology now includes a greater understanding of its ability to both directly promote tumour growth and indirectly create a nurturing local tumour microenvironment, as well as insight into the genetic regulation of MIF expression. Increasingly, this evidence highlights MIF, as a prime therapeutic target in patients with augmented inflammatory responses that predispose to cancer development.

Conflict of interest: None declared.

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