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Mini review

Macrophage migration inhibitory factor: A key cytokine and therapeutic target in colon cancer

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ABSTRACT

Macrophage migration inhibitory factor (MIF) was one of the first cytokines to be discovered, over 40 years ago. Since that time a burgeoning interest has developed in the role that MIF plays in both the regulation of normal physiology and the response to pathology. MIF is a pleotropic cytokine that functions to promote inflammation, drive cellular proliferation, inhibit apoptosis and regulate the migration and activation state of immune cells. These functions are particularly relevant for the development of cancer and it is notable that various solid tumours over express MIF. This includes tumours of the gastrointestinal tract and MIF appears to play a particularly prominent role in the development and progression of colonic adenocarcinoma. Here we review the role that MIF plays in colonic carcinogenesis through the promotion of colonic inflammation, as well as the progression of primary and metastatic colon cancer. The recent development of various antagonists and antibodies that inhibit MIF activity indicates that we may soon be able to classify MIF as a therapeutic target in colon cancer patients.

1. Introduction

Throughout Europe, colorectal cancer is the third most commonly diagnosed cancer in men and women combined [1], responsible for an estimated 150,000 cancer deaths in 2012 [1]. Chronic inflammation is recognised as an important contributing factor to the development of colorectal cancer. Patients with inflammatory bowel disease (IBD) have a significantly higher risk of colon cancer when compared with healthy populations [2–4]. Furthermore, the long-term administration of low-dose dextran sulphate sodium (DSS) to mice or rats results in chronic colonic inflammation which can progresses to colon cancer [5], indicating that colonic inflammation can pre-date malignancy within the colon. The carcinogenic effect of DSS is inhibited when mice are treated with various immunosuppressive agents [6,7], demonstrating the importance of the immune system in the promotion of colon cancer. Equally, patients with cardiovascular disease who are treated with low-dose anti-inflammatory medication have a reduced colon cancer risk [8,9]. In short, colonic inflammation and cancer are inextricably linked.

Cytokines are strongly implicated in the development of cancer within chronically inflamed tissues. Certain cytokines promote the development of a pro-tumourigenic microenvironment by orchestrating the recruitment of immune cells, as well as having direct effects on tumour, endothelial and stromal cells in order to promote cancer development and progression [10]. Of the cytokines displaying pro-tumourigenic activity, the pleiotropic molecule macrophage inhibitory factor (MIF) has received particular attention [11,12]. Indeed, the efficacy of MIF inhibition has been demonstrated in numerous pre-clinical models of both inflammatory and malignant disease (Table 1). This highly studied molecule displays an array of biological functions, many of which are capable of driving cancer progression. These functions have been studied in detail using *in vitro* and pre-clinical models of colon cancer. With this in mind, we review the current experimental and clinical data linking MIF expression to the development and progression of colon cancer and thus provide support for developing clinical trials of MIF inhibitors in colon cancer patients.

2. Biology of macrophage inhibitory factor

2.1. MIF gene and protein structure

MIF was one of the first cytokines to be discovered, when its production by T-lymphocytes was demonstrated to inhibit the

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Table 1
Effect of MIF inhibition in various pre-clinical disease models. Intraperitoneal [IP], oral [PO].

Condition	Murine model	MIF inhibitor [route]	Effect of MIF inhibition	References
Colon cancer	Caecal implantation	ISO1 [IP] MIF neutralising antibody [IP] ISO-66 (ISO analogue)	Reduced tumour weight and volume Reduced hepatic metastasis incidence Reduction in tumour burden	[106] [125]
	Subcutaneous implantation of CT26 colon cancer cells	Anti-rat polyclonal MIF neutralising antibody	Reduction in tumour growth Reduction in tumour angiogenesis	[66]
IBD	DSS-induced colitis	ISO-F (fluorinated analogue of ISO-1) [PO]	Reduction in histological colitis score and disease activity Increased mouse weight	[126]
	DSS-induced colitis	Polyclonal MIF neutralising antibody [IP]	Reduction in histological colitis score and disease activity	[75]
	Intrarectal 2,4,6 trinitro-benzenesulphonic acid	Monoclonal MIF neutralising antibody [IP]	Reduction in colonic myeloperoxidase activity and TNFα level	[127]
Rheumatoid arthritis	Anti-type II collagen antibody/LPS-induced arthritis	Polyclonal MIF neutralising antibody [IP]	Reduction in histological arthritis score Reduction in intra-codylar MMP13	[128,129]
Sepsis	LPS administration Caecal ligation and puncture	ISO-1 [IP]	Reduction in TNFα release by macrophages Increased survival	[130]
Multiple sclerosis	Experimental autoimmune encephalitis	Small molecule MIF inhibitors (CPSI-1306 and CPSI-2705) [PO]	Reduction in clinical signs Increased spinal cord regulatory T-cell count	[131]
	Experimental autoimmune encephalitis	Monoclonal MIF neutralising antibody [IP]	Reduction in histological severity score Reduction in central nervous system VCAM expression	[132]
Bronchopulmonary dysplasia	Exposure of transgenic mouse demonstrating pulmonary MIF over-expression to hyperoxia	MIF 098 (small molecule inhibitor) [IP]	Improved alveolar architecture	[133]
Diabetes	Stroptazocin-induced diabetes	ISO-1 [IP] MIF neutralising antibody [IP]	Reduction in circulating TNFα, INFγ and nitric oxide concentration Reduction in hypoglycaemia	[134]
Atherosclerosis	Apolipoprotein E-deficient ($ApoE^{-/-}$) mice	Monoclonal MIF neutralising antibody [IP]	Reduction in intimal macrophage count Reduction in plasma fibrinogen and IL-6 concentrations Reduction in plaque volume	[135]
Asthma	Ovalbumin-immunized rat asthma model	Polyclonal MIF neutralising antibody [IP]	Reduction in pulmonary eosinophil and neutrophil counts Reduction in airway pressure	[136]
	Ovalbumin-immunized mouse asthma model	Anti-rat polyclonal MIF neutralising antibody [IP]	Reduction in pulmonary eosinophil and neutrophil counts Reduction in airway hyper-responsiveness	[137,138]

random migration of guinea pig macrophages [13,14]. Despite this discovery almost 50 years ago, the MIF cDNA sequence – determined through functional expression cloning of a cDNA library prepared from activated T-cells – was not identified until 1989 [15]. The MIF gene resides on chromosome 22 and is highly conserved between mouse and human [16,17]. Interestingly, a homologue of the human MIF gene has also been identified in parasites [18,19], where the protein product is thought to serve a protective function [19]. Indeed, widespread MIF gene homology across various species of animal, parasite and plant suggests that the protein may serve a fundamental biological role [16].

Recombinant MIF was first produced in 1993 [20], a breakthrough that led to increased understanding of both its structure and function. The MIF protein is relatively small (12.5 kDa), lacking a conventional N-terminal leader sequence and is therefore released from the cell by a leaderless secretion pathway [17]. MIF shares considerable amino acid sequence homology with the enzyme D-dopachrometautomerase [21] and possesses similar catalytic activity [21]. The tertiary structure of the monomeric MIF protein was determined using X-ray crystallography in 1996 [22,23] (Fig. 1). A MIF monomer consists of two anti-parallel α-helices, four β-strands forming a β-sheet and a further two singular β-strands [24]. MIF exists in dimeric and homo-trimeric states under physiological conditions [24]. Trimeric MIF is arranged to produce an inner, hydrophobic pore [24] and this structure appears particularly important for maintenance of the proteins enzymatic function [25–27].

Broadly speaking, amino acid residues at the C-terminus of the protein are important for enzymatic activity [28], whilst those at the N-terminus end appear to be involved in chemokine receptor binding [29]. Proline-1, found towards the C-terminus, in particular is important for maintaining the enzymatic activity of the protein [30]. Conversely, mutation at Aspartic acid-44 or Arginine-11 on adjacent MIF monomers within the trimeric protein reduces the proteins chemoattractant properties [31] (Fig. 1).

2.2. MIF function

2.2.1. Enzyme function

MIFs catalytic activity includes both tautomerisation [32] and oxidoreduction [33]. The pathophysiological significance of such enzymatic activity is unclear, as the majority of identified MIF substrates are not present at physiologically relevant concentrations *in vivo*. Nonetheless, Mutational analyses and the use of specific MIF inhibitors indicate that MIF's enzymatic site is required for many of the protein's biological functions, including anti-gluocorticoid activity [26,30,34].

2.2.2. Hormone function

The first indication of MIFs hormone function came from the analysis of cultured pituitary cells, which were found to express high MIF levels following lipopolysaccharide (LPS) stimulation [20]. This was a surprising finding, given that cells of the anterior

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