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Review

The non-mammalian MIF superfamily

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ABSTRACT

Macrophage migration inhibitory factor (MIF) was first described as a cytokine 50 years ago, and emerged in mammals as a pleiotropic protein with pro-inflammatory, chemotactic, and growth-promoting activities. In addition, MIF has gained substantial attention as a pivotal upstream mediator of innate and adaptive immune responses and with pathologic roles in several diseases. Of less importance in mammals is an intrinsic but non-physiologic enzymatic activity that points to MIF's evolution from an ancient defense molecule. Therefore, it is not surprising that *mif*-like genes also have been found across a range of different organisms including bacteria, plants, protozoa, helminths, molluscs, arthropods, fish, amphibians and birds. While Genebank analysis identifying *mif*-like genes across species is extensive, contained herein is an overview of the non-mammalian MIF-like proteins that have been most well studied experimentally. For many of these organisms, MIF contributes to an innate defense system or plays a role in development. For parasitic organisms however, MIF appears to function as a virulence factor aiding in the establishment or persistence of infection by modulating the host immune response. Consequently, a combined targeting of both parasitic and host MIF could lead to more effective treatment strategies for parasitic diseases of socioeconomic importance.

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1. Introduction: mammalian MIF

Macrophage migration inhibitory factor (MIF) has proven to be an intriguing molecule of study for many scientists. Originally described as a cytokine over 50 years ago, MIF has been found in mammals to be a pleiotropic cytokine/chemokine with unique characteristics that have led to it being coined the "most interesting factor" (Bucala, 2000). Immunologically, MIF has gained substantial attention as a pivotal upstream mediator of innate and adaptive immune responses (Flaster et al., 2007) and has been implicated

Abbreviations: MIF, macrophage migrating inhibitory factor; ISO-1, (S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester; MDL, MIF/D-DT like.

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in many infectious, inflammatory, and immune diseases including septic shock, colitis, malaria, rheumatoid arthritis, atherosclerosis, and tumorigenesis (Bucala and Donnelly, 2007; Bernhagen et al., 1993; Mikulowska et al., 1997; Bozza et al., 2012). Being present within the cytosol of most cells as preformed protein, MIF mediates several of its effects via an autocrine/paracrine signaling pathway leading to (i) the activation of ERK1/ERK2 MAP kinases, the triggering of downstream pro-inflammatory gene expression (e.g. TNF-α, IL-1β, IL-6, IL-8 and IL-12) and production of matrix metalloproteases, cyclooxygenase 2 and prostaglandin E_2, (ii) up-regulation of TLR4 expression, (iii) suppression of p53 activity, (iv) counter-regulation of the anti-inflammatory and immunosuppressive effects of glucocorticoids, and (v) regulation of cell cycling (Bozza et al., 2012; Calandra and Roger, 2003; Lue et al., 2002; Leng and Bucala, 2006). In addition, MIF triggers calcium influx and integrin activation, and modulates lymphocyte/myeloid cell activation and trafficking as reviewed by Bernhagen et al. (Bernhagen et al., 2007). Secreted/released MIF can exert its functions via four cell surface receptor proteins. On one hand, MIF signals through CD74, which is a type II receptor protein whose intracellular form (i.e. the invariant chain, Ii) functions in the transport of class II proteins from the endoplasmic reticulum to the Golgi and a surface form (~2–5% of CD74) that functions independently of class II to bind extracellular MIF with nM affinity for internalization. On the other hand, MIF is also a non-cognate ligand for the CXC chemokine receptors CXCR2, CXCR4, and CXCR7 (Bernhagen et al., 2007; Leng et al., 2003; Alampour-Rajabi et al., 2015; Schröder, 2016), mediating interactions that may be facilitated by CD74.

In addition to its receptor-mediated signalling activities, i.e. inhibiting the random migration of cells and promoting downstream cytokine production, MIF harbors two evolutionally conserved catalytic activities that provide it with additional functional complexity. Mammalian MIF can be demonstrated to exhibit a thiol-protein oxidoreductase activity by virtue of a thioredoxin-like CXXC motif (Kleemann et al., 1998) and a keto-enol tautomerase activity catalyzed by an N-terminal proline that can tautomerize model substrates such as D-dopachrome, hydroxyplenylpyruvate or phenylpyruvate (Calandra and Roger, 2003; Rosengren et al., 1996, 1997). It is unclear however whether these MIF enzymatic activities have true functional relevance in mammals, but with respect to keto-enol tautomerization the N-terminal proline is strictly conserved among all known MIF proteins. The enzymatic tautomerization of the physiologic substrate L-dopachrome mediates the primitive invertebrate defense pathway known as melanotic encapsulation, however, MIF is only active against the non-physiologic stereoisomer D-dopachrome. A genetically-engineered knock-in mouse in which endogenous MIF was replaced by a catalytically-inactive MIF^{P1G} demonstrated a phenotype intermediate between that of wild type and *mif* gene deficient mice. Given that MIF^{P1G} binds to CD74 with lower affinity than wild type MIF, these observations are consistent with the interpretation that the MIF tautomerase activity is dispensable for biologic function but that structural features imparted by Pro1 are essential for receptor binding and activation (Fingerle-Rowson et al., 2009).

Biologically active MIF exists as a homo-trimer with dimensions of 35 Å × 50 Å × 50 Å, forming an αβ structure with α-helices surrounding β-sheets that completely wrap around to form a barrel with open ends forming a solvent channel, whereby each monomer consists of a βαββββαββ motif (Sun et al., 1996). This protein fold defines the MIF structural superfamily. The tautomerase active site within the MIF protein is situated at the interface between pairs of subunits (lined by amino acid residues 1, 33–34, and 64–66) and the overall substrate binding site is highly conserved among MIF homologues. In contrast, the residues necessary for the protein-thiol oxidoreductase activity, which is associated with a CXXC motif in mammalian MIF, are less conserved among invertebrate species.

Interestingly, within the mammalian genome there is a single gene that is homologous to the *mif* gene, which encodes a protein called D-dopachrome tautomerase (D-DT). While first described in literature in the early 1990s, few functional studies of D-DT were published until the last five years (Odh et al., 1993). Despite a low amino acid sequence identity between MIF and D-DT (34% in humans and 27% in mice), there is a significant three dimensional structural homology with MIF (Sugimoto et al., 1999). As reviewed by Merk et al. (Merk et al., 2012), like MIF, D-DT (sometimes also referred to as mammalian MIF-2) is present in most tissues and exists in pre-formed pools, it is released upon stimulation and also binds to the receptor complex CD74/CD44, leading to a similar signal transduction cascade as MIF. Yet, D-DT may be less biologically active than MIF: it binds CD74 with a ~3-fold higher association rate (k_a) but a ~11-fold faster dissociation rate (k_d) than MIF. This potentially lower potency of D-DT might lead to partial antagonism in circumstances where high concentrations of MIF are produced (Merk et al., 2011).

2. Non-mammalian MIF homologues identified throughout the eubacteria, animal and plant kingdoms

Given that MIF is an evolutionary ancient molecule, it is not surprising that genes encoding proteins that appear related to the mammalian MIF superfamily members (i.e. *mif* and its paralogue *d-dt*) have been found in different prokaryotes (e.g. bacterial cells) and eukaryotes (e.g. plants, vertebrates such as fish, amphibians, birds and mammals and invertebrates such as protozoa, helminths, nematodes, molluscs and arthropods). While Genebank analysis identifying *mif*-like genes across species is extensive, it should be noted that genomic databases primarily reflect sequences present in euchromatin and it remains possible that *mif*-related genes exist in heterochromatin. Contained herein is an overview of the most well studied/cloned non-mammalian homologues of MIF and D-DT (Table 1).

Regarding the role of bacterial MIF homologues, so far only in the marine Cyanobacterium *Prochlorococcus marinus* a MIF homologue has been identified, the protein crystalized, and found to have tautomerase activity. More detailed studies will be required to address whether a MIF-like protein from a free-living bacterium possesses immunoregulatory features similar to those of mammalian MIF (Wasiel et al., 2010).

Three MIF/DDT-like (MDL) polypeptides [*Ath*-MDL-1 (At5g57170), *Ath*-MDL-2 (At5g01650) and *Ath*-MDL-3 (At3g51660)] have been identified by *in silico* analysis in the plant *Arabidopsis thaliana* and their function are currently under investigation. Given that plants lack a circulation/extracellular space-based mobile immune defense system, these plant MIF homologues most likely exert intracellular effects. Hereby, the suggested presence of a tautomerase activity might be of importance. D-dopachrome is an artificial substrate of mammalian MIF and other MDLs and is a cyclization product of D-3,4-dihydroxyphenylalanine (also known as D-DOPA), suggesting a role in the biosynthesis of melanin-type pigments. While plants lack conventional melanin, they synthesize catechol melanin, which is chemically related to L-DOPA and might serve a role as precursor of different secondary plant metabolites (melanin) (Solano, 2014; Soares et al., 2014).

With respect to different vertebrate MIF homologues, they appear universally to be involved in innate and adaptive immune responses and affect cell migration, pro-inflammatory cytokine secretion, and cell differentiation or morphogenesis (Bozza et al., 2012). In invertebrates such as molluscs and arthropods, which