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Post-translational regulation of macrophage migration inhibitory factor: Basis for functional fine-tuning

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ABSTRACT

Macrophage migration inhibitory factor (MIF) is a chemokine-like protein and an important mediator in the inflammatory response. Unlike most other pro-inflammatory cytokines, a number of cell types constitutively express MIF and secretion occurs from preformed stores. MIF is an evolutionarily conserved protein that shows a remarkable functional diversity, including specific binding to surface CD74 and chemokine receptors and the presence of two intrinsic tautomerase and oxidoreductase activities. Several studies have shown that MIF is subject to post-translational modification, particularly redox-dependent modification of the catalytic proline and cysteine residues. In this review, we summarize and discuss MIF post-translational modifications and their effects on the biological properties of this protein. We propose that the redox-sensitive residues in MIF will be modified at sites of inflammation and that this will add further depth to the functional diversity of this intriguing cytokine.

1. Introduction

Identified in 1966, macrophage migration inhibitory factor (MIF) was initially shown to inhibit the random migration of macrophages upon its release from T lymphocytes during a delayed-type hypersensitivity response [1,2]. Today, MIF is widely recognized as a critical upstream player in the innate immune response, where it triggers and amplifies cytokine production by stimulating the production of pro-inflammatory mediators, such as TNF-α, interferon-γ, interleukins (IL-1β, IL-2, IL-6, IL-8), nitric oxide, prostaglandin E_2 and tissue-degrading matrix metalloproteinases [3–6]. MIF also promotes inflammation by orchestrating leukocyte trafficking [7], inhibiting p53-mediated apoptosis of inflammatory cells sustaining their survival span [8,9], and by counter-regulating the immunosuppressive action of glucocorticoids [10,11]. Furthermore, MIF exhibits tumor growth-promoting properties [12,13].

Given its broad pro-inflammatory activities, it is not surprising that MIF is implicated in acute and chronic inflammatory diseases such as rheumatoid arthritis, asthma, diabetes, sepsis, cancer, atherosclerosis and other cardiovascular diseases [8,14–22]. MIF is released from different immune cell types including monocytes, macrophages, neutrophils, T cells, B cells, dendritic cells, and eosinophils, but secretion can also occur from certain endocrine, endothelial and epithelial cells upon inflammatory stimulation or injury [23,24]. MIF consists of 114 amino acids and has a molecular mass of 12,345 Da, with a 90% sequence homology between human and murine MIF. The sequence of rat and mouse MIF only differ in a single amino acid [25]. More recently, a genetic homolog of MIF, termed D-dopachrome tautomerase (D-DT) or MIF-2, was identified and found to play role in the inflammatory response [26,27].

MIF binds to the chemokine receptors CXCR4 and CXCR2 [28,29] to foster inflammatory and atherogenic monocyte/neutrophil and T cell chemotaxis, respectively, and is therefore classified as a chemokine-like function (CLF) or atypical (ACK) chemokine [30]. In light of the discovery of MIF's chemokine activity, it appears that the eponymous 'migration-inhibitory effect' represents a chemokinetic effect of MIF on random leukocyte motility [30]. MIF also binds to the type II transmembrane protein CD74, which leads to intramembranous cleavage ('RIP') and signaling and/or co-activation of CD44 [31–33], while CD74/CXCR complexes also have been implicated in MIF signaling responses in atherosclerosis [29]. Following receptor activation, MIF facilitates cell proliferation, inhibition of apoptosis and migration of immune cells via the ERK1/2 MAP kinase, Gαi and PI3K/AKT pathway [29,32].

MIF is widely considered to act as a key-regulator in myocardial ischemia/reperfusion injury, where MIF is released in two waves

Abbreviations: GIF, glycosylation inhibiting factor; MIF, macrophage migration inhibitory factor; MPO, myeloperoxidase; TPOR, thiol-protein oxidoreductase

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[34,35]. MIF release during the first wave in the early stage of ischemia is thought to stem from the ischaemic myocardium and to adopt a protective function [34,35]. On a molecular basis, MIF's protective activity is due to its ability to inhibit the apoptosis-inducing c-Jun *N*-terminal kinase (JNK) pathway and to reduce oxidative stress to the myocardium generated during ischemia/reperfusion [36,37]. Importantly, MIF released from the ischaemic heart can induce AMPK activation via binding to CD74, which promotes glucose uptake and protects the heart during ischemia/reperfusion by metabolic pathways [17,38]. The second MIF wave is that of pro-inflammatory MIF released from activated infiltrating immune cells including monocytes [34]. Therefore, MIF can have multiple and sometimes opposing functions depending on the cellular source and the time of release. The mechanisms for regulating MIF function and the mechanistic details of the fine-tuning between cell types and phases are currently unclear.

MIF differs from other pro-inflammatory cytokines by being semi-constitutively expressed and secreted into circulation rather than being regulated by a surge in transcriptional activity in response to inflammatory stimuli [39–41]. MIF forms homo-trimer [42,43] and, unlike other common known cytokines, has two evolutionarily conserved catalytic activities – a tautomerase and a thiol-protein oxidoreductase (TPOR) activity – that are carried out by two distinct catalytic centres (Fig. 1). The TPOR activity of MIF is mediated through a conserved CALC motif containing Cys-57 and Cys-60 [44] and has been shown to catalyse the reduction of insulin and 2-hydroxyethyldisulfide (HED) and to be involved in cellular redox protection [44–46]. The tautomerase activity is facilitated by the conserved *N*-terminal proline, which acts as a catalytic nucleophile at physiological pH due to its unusually low pKa of 5.6 [47].

The function of the tautomerase activity is unknown and a physiological substrate has yet to be identified. However, the region encompassing the *N*-terminal proline is involved in receptor binding and it has been shown that targeting the *N*-terminal proline with small molecule inhibitors can inhibit some of the pro-inflammatory activities of MIF [48–53]. Targeting the tautomerase active site is thus currently being explored as an anti-inflammatory treatment avenue [53].

Apart from pharmacological electrophiles, the *N*-terminal proline has been shown to react with physiological oxidants/electrophiles generated by the neutrophil-derived enzyme myeloperoxidase [54]. Indeed, the inflammatory environment with an array of reactive oxygen and nitrogen species being produced by phagocytic cells makes modifications of redox-sensitive proteins highly likely.

We hypothesize that these post-translational modifications play an important role in the regulation of MIF.

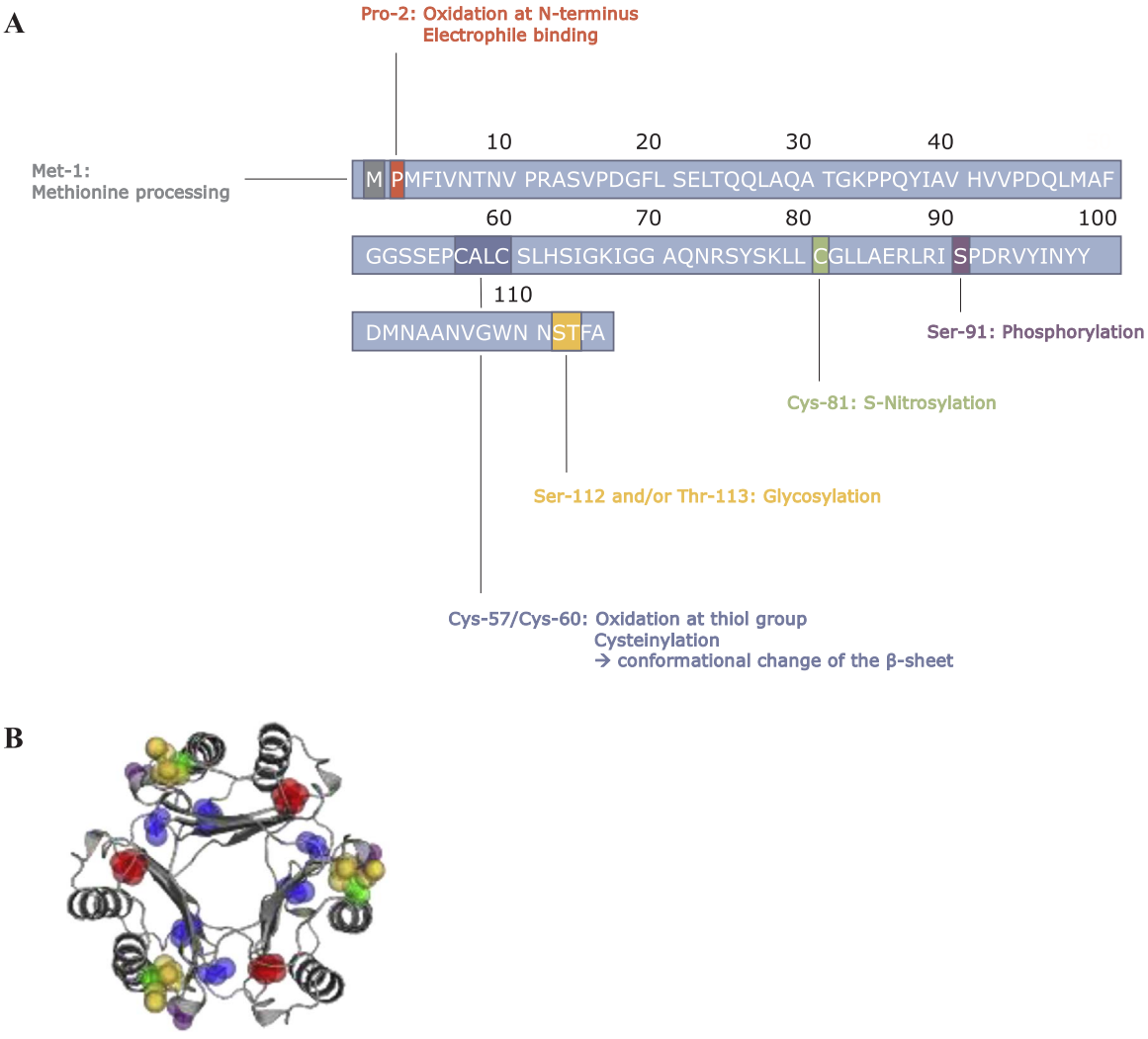

Fig. 1. A) Amino acid sequence of MIF with residues targeted for post-translational modifications highlighted in colour. *Note*: the suggested cysteine-oxidized form is speculative and lacks structural confirmation. **B)** Ribbon structure of the MIF trimer based in the PDB crystal structure 3DJH (1.25 Å resolution) [96] with the side chain susceptible to post-translational modifications shown in coloured spheres: red – Pro-2, blue – Cys-57/Cys-60, green – Cys-81, purple – Ser-91, orange yellow – Ser-112/Thr-113. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)