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Review Article

Macrophage migration inhibitory factor: A multifaceted cytokine implicated in multiple neurological diseases

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ABSTRACT

Macrophage migration inhibitory factor (MIF) is a conserved cytokine found as a homotrimer protein. It is found in a wide spectrum of cell types in the body including neuronal and non-neuronal cells. MIF is implicated in several biological processes; chemo-attraction, cytokine activity, and receptor binding, among other functions. More recently, a chaperone-like activity has been added to its repertoire. In this review, we focus on the implication of MIF in the central nervous system and peripheries, its role in neurological disorders, and the mechanisms by which MIF is regulated. Numerous studies have associated MIF with various disease settings. MIF plays an important role in advocating tumorigenic processes, Alzheimer's disease, and is also upregulated in autism-spectrum disorders and spinal cord injury where it contributes to the severity of the injured area. The protective effect of MIF has been reported in amyotrophic lateral sclerosis by its reduction of aggregated misfolded SOD1, subsequently reducing the severity of this disease. Interestingly, a protective as well as pathological role for MIF has been implicated in stroke and cerebral ischemia, as well as depression. Thus, the role of MIF in neurological disorders appears to be diverse with both beneficial and adversary effects. Furthermore, its modulation is rather complex and it is regulated by different proteins, either on a molecular or protein level. This complexity might be dependent on the pathophysiological context and/or cellular microenvironment. Hence, further clarification of its diverse roles in neurological pathologies is warranted to provide new mechanistic insights which may lead in the future to the development of therapeutic strategies based on MIF, to fight some of these neurological disorders.

Contents

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1. MIF structure and function

Macrophage migration inhibitory factor (MIF) exists predominantly as a homotrimer. Each monomer consists of a 114 amino acid residue (MW ~ 12.3 kDa), α/β structure composed of two antiparallel α-helices packed against a four-stranded β-sheet (Sun et al., 1996; El-Turk et al., 2008; Crichlow et al., 2009). The monomer has an additional two β-strands that interact with the β-sheets of adjacent subunits to form the interface between monomers. The three β-sheets are arranged to form a barrel containing a solvent-accessible channel that runs through the center of the protein along a molecular 3-fold axis. Electrostatic potential maps reveal that the channel has a positive potential, suggesting that it binds negatively charged molecules (Sun et al., 1996).

It has been shown that MIF is an evolutionarily conserved cytokine (Nishihira et al., 1995; Du et al., 2004), which is expressed not only in the immune system but also ubiquitously expressed by a variety of other cells including monocytes, macrophages, fibroblasts, insulin secreting β-cells of the pancreas, pituitary cells, endothelial cells (Calandra and Roger, 2003), neurons, non-neuronal cells and neural stem cell progenitors (Suzuki et al., 1999; Koda et al., 2004; Choi et al., 2014).

The MIF superfamily consists of MIF and the recently identified homolog D-dopachrome tautomerase (D-DT or MIF-2). Both genes are located in close proximity to each other on chromosome 22q11.23 (Merk et al., 2012). D-DT demonstrates a similar tautomerase activity to MIF (Sugimoto et al., 1999), and later was shown to share also biological similarities (Coleman et al., 2008; Xin et al., 2010; Merk et al., 2011; Roger et al., 2017).

MIF was the first lymphokine shown to prevent the pro-inflammatory migration of macrophages out of capillary tubes (Bloom and Bennett, 1966; David, 1966). Since these initial findings, MIF's functions have been greatly expanded and its involvement in a wide range of physiological processes has been reported. It has been shown to have both chemoattractant (Gao et al., 2011) and cytokine activity (Dimitriu et al., 1974) as well as receptor binding (Leu et al., 1972; Shi et al., 2006). MIF binds to HLA class II histocompatibility antigen gamma chain also known as Cluster of Differentiation 74 (CD74). The phosphorylation of CD74 through MIF binding leads to downstream signaling mediated by activation of CD44 (Leng et al., 2003). In steady state, a small fraction of CD74 is expressed on the cell surface (Wraight et al., 1990). CD74/CD44 complex initiates a signaling cascade that leads to cell survival (Leng et al., 2003). Specifically, MIF binding to the CD74/CD44 complex regulates mature B cell maintenance, proliferation and survival by facilitating entry into the S-phase of the cell cycle and elevation of cyclin E levels, resulting in cell proliferation, followed by a cascade that augments the expression of the survival genes, Bcl-XL and Bcl-2 (Bucala and Shachar, 2014).

Additionally, studies have revealed that CD74 cleavage upon binding of MIF releases CD74 cytosolic intracellular domain (CD74-ICD) (Matza et al., 2002; Becker-Herman et al., 2005). CD74-ICD has been found to bind to chromatin, and to induce cell survival and cell-cell signaling cascade (Gil-Yarom et al., 2017). The MIF homolog MIF-2 also demonstrates receptor binding to CD74 (Merk et al., 2011) and possibly activates the inflammatory cascade downstream to CD74 (Kim et al., 2016; Kim et al., 2017; Ochi et al., 2017; Tilstam et al., 2017). Further studies on MIF and MIF-2 are warranted to clarify and to address their similarities.

MIF is also a functional noncognate ligand for the chemokine receptors CXCR2/4 controlling inflammatory and atherogenic cell recruitment (Bernhagen et al., 2007). Moreover, MIF has been implicated in several pathological processes, among them; inflammatory diseases, such as atherosclerosis and rheumatoid arthritis (Li et al., 2006), autoimmune diseases (Assis et al., 2016) and tumor growth (Mitchell and Bucala, 2000). Additionally, its role in dopachrome isomerase activity (Crichlow et al., 2007), phenylpyruvate tautomerase activity (Wilson et al., 2005) and protein binding (Shen et al., 2003) has been revealed. More recently, its chaperone-like function (Cherepkova et al., 2006; Israelson et al., 2015) and a PARP-1-dependent endonuclease activity have been reported (Wang et al., 2016). A further expansion on its involvement in the central nervous system (CNS) and the periphery will follow shortly (Fig. 1).

2. MIF expression in the central nervous system

Since the establishment of its role in the immune and inflammatory responses, emerging data have also identified a role for MIF in the physiology of the CNS and as a neuro immuno-modulator. Firstly, MIF has been identified as an important component of the endocrine system and the hypothalamic-pituitary-adrenal axis, expressed constitutively by the anterior lobe of the pituitary gland and released to the circulation on stress or inflammation stimuli (Bernhagen et al., 1993; Nishino et al., 1995; Calandra and Roger, 2003). It is also expressed in the aldosterone- and glucocorticoid-producing epithelial cells of the adrenal cortex (Fingerle-Rowson et al., 2003a; Leng et al., 2009). MIF's level rises together with adrenocorticotrophic hormone (ACTH) in response to stress or invasive stimuli. ACTH serves to stimulate adrenal glucocorticoid production while MIF acts to counter-regulate the immunosuppressive action of glucocorticoids (Bernhagen et al., 1993; Calandra et al., 1995; Flaster et al., 2007). As far back as the 90s MIF was reported to be isolated from whole bovine brain cytosol (Galat et al., 1993). Studies carried out on rats also reported a strong baseline expression of MIF in the neurons of the rat cortex, hypothalamus, hippocampus, cerebellum and pons, with protein expression mainly in the terminal fields associated with the neurons (Bacher et al., 1998). MIF was also highly expressed within mossy fibers of the dentate gyrus and hippocampal dendrites structures, and was shown to be involved in glucocorticoid-induced tissue damage, suggesting an association between MIF and targets of glucocorticoid action. Furthermore, its expression can be upregulated by inflammatory stimuli as was observed in neurons and in macrophages following intracranial Lipopolysaccharide-Related Stimuli (LPS) (Bacher et al., 1998). An additional player in MIF upregulation is Angiotensin II (Ang II), which up-regulates MIF mRNA production and MIF protein secretion by tubular epithelial cells (Rice et al., 2003). Ang II also upregulates MIF expression in primary neuronal cultures from hypothalamus and brainstem of normotensive rats. Surprisingly, CNS injections of Ang II in normotensive rats increased MIF expression in the paraventricular nucleus (PVN) of the hypothalamus, an area that plays a key role in regulating sympathetic outflow and hypothalamus/pituitary axis activity (Harrison and Sumners, 2009). Ang II activity is predominantly mediated by type 1 Ang II receptor (AT1R) and subsequent activation of various signaling cascades including NADPH oxidase and resultant reactive oxygen species (ROS) (Patel and Schultz, 2012; Jang et al., 2015). Increased levels of ROS lead to superoxide production, and in turn further activation of superoxide dismutase (SOD1) is needed to reduce ROS levels (Rhee et al., 2005). Additionally, ROS also regulates MIF expression in neurons. This can be seen in primary motor neurons exposed to hydrogen peroxide (H_2O_2), an exogenous ROS. When the oxidative action of H_2O_2 is attenuated, the levels of MIF are reduced (Harrison and Sumners, 2009). Additionally, MIF was observed in microglia as well as in cerebrospinal fluid (CSF) and its levels are also elevated following LPS stimuli. MIF has been shown to promote the growth of neuronal progenitors *in vitro* (Schwarz et al., 1998), indicative of a possible role in growth promotion in certain cell types. However, it is important to note that evidence exists for detrimental effects of MIF elevation in CSF of Alzheimer's patients (Bacher et al., 2003).

One of the main barriers that protect the CNS from damage is the meninges, a complex multilayer cover made of meningothelial cells (MEC). Studies on the protective effects executed by these cells have shown that MEC are capable of digesting apoptotic cells preventing further inflammation and that this uptake is followed by an increase in IL-1, IL-16 and MIF (Li et al., 2014), supporting a necessity for MIF as a mediator in the inflammatory zone.

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