An integrated signal transduction network of macrophage migration inhibitory factor

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Abstract Macrophage migration inhibitory factor (MIF) is a glycosylated multi-functional protein that acts as an enzyme as well as a cytokine. MIF mediates its actions through a cell surface class II major histocompatibility chaperone, CD74 and co-receptors such as CD44, CXCR2, CXCR4 or CXCR7. MIF has been implicated in the pathogenesis of several acute and chronic inflammatory diseases. Although MIF is a molecule of biomedical importance, a public resource of MIF signaling pathway is currently lacking. In view of this, we carried out detailed data mining and documentation of the signaling events pertaining to MIF from published literature and developed an integrated reaction map of MIF signaling. This resulted in the cataloguing of 68 molecules belonging to MIF signaling pathway, which includes 24 protein-protein

interactions, 44 post-translational modifications, 11 protein translocation events and 8 activation/inhibition events. In addition, 65 gene regulation events at the mRNA levels induced by MIF signaling have also been catalogued. This signaling pathway has been integrated into NetPath (<http://www.netpath.org>), a freely available human signaling pathway resource developed previously by our group. The MIF pathway data is freely available online in various community standard data exchange formats. We expect that data on signaling events and a detailed signaling map of MIF will provide the scientific community with an improved platform to facilitate further molecular as well as biomedical investigations on MIF.

Keywords Immune response · Inflammation · NetSlim · Pro-inflammatory cytokine · Post-translational modifications · Protein-protein interactions

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Abbreviations

MIF	Macrophage migration inhibitory factor
PPI	Protein-protein interaction
PTM	Post-translational modification
HPRD	Human Protein Reference Database
SBML	Systems Biology Markup Language
PSI-MI	Proteomics Standards Initiative for Molecular Interaction
BioPAX	Biological Pathway Exchange

Introduction

Macrophage migration inhibitory factor (MIF), also known as glycosylation-inhibitory factor, is an evolutionarily-conserved, 115 amino acid non-glycosylated protein of 12.5 kDa (Weiser et al. 1989; Bernhagen et al. 1994). This pro-inflammatory

cytokine is coded by the MIF gene located on chromosome 22 (22q11.2) in humans. It was one of the first cytokines to be identified (Bloom and Bennett 1966; David 1966). In spite of its discovery in 1966, its biological function remained ambiguous until the human MIF complementary DNA was cloned from T cells in the year 1989 (Weiser et al. 1989). Three-dimensional structural analyses revealed that MIF exists as a homotrimer and a catalytic site is located between two adjacent monomers of the homotrimer (Sun et al. 1996). Initially, MIF was thought to be predominantly expressed by T cells. Later, other immune cells such as monocytes, macrophages, basophils, eosinophils, neutrophils, B cells, mast cells and dendritic cells were shown to express MIF. In addition to the immune system, MIF is also expressed in the brain, eye, ear, lungs, breast, endocrine system, liver, testis, prostate, ovaries, gastrointestinal tract, kidney, skin, bones and joints (Calandra and Roger 2003). MIF is a multi-functional protein that operates as a cytokine and an enzyme. MIF, as an enzyme, can mediate D-dopachrome tautomerase, phenylpyruvate keto-enol isomerase and thiol-protein oxidoreductase activity (Rosengren et al. 1996; Rosengren et al. 1997; Kleemann et al. 1998). MIF, as a cytokine, is a mediator of innate immunity and major regulator of inflammation (Calandra et al. 1995).

MIF exerts its action through binding to its cognate receptors in the target cells and activating downstream signaling leading to the regulation of gene transcription and subsequent expression of effector molecules. The first MIF receptor to be identified is a cell surface class II major histocompatibility chaperone, CD74. MIF binds to CD74 with high affinity (Leng et al. 2003). In addition to CD74, MIF signaling requires co-receptors such as CD44, CXCR2, CXCR4 or CXCR7 (Shi et al. 2006; Bernhagen et al. 2007; Tarnowski et al. 2010). MIF signals in both an autocrine and paracrine fashion. MIF signaling via CD74/CD44 involves phosphorylation of serine residues in the cytoplasmic tails of CD74 and CD44 followed by recruitment of a non-receptor tyrosine kinase, SRC (Shi et al. 2006). MIF has been shown to mediate its biological effects via two signaling mechanisms: the classical receptor-mediated pathway and a non-classical endocytic pathway. MIF exerts its functions through activation of several signaling pathways including mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT) and phospholipase A2 (PLA2)/arachidonic acid pathways (Tillmann et al. 2013).

MIF plays a pivotal role in innate as well as acquired immunity. MIF is an important component of the host inflammatory response. The concentration of circulating MIF is increased during inflammation, infection and stress (Calandra et al. 2000). MIF has been shown to directly or indirectly promote the expression of pro-inflammatory cytokines including TNF, IFN- γ , IL-1 β , IL-2, IL-6 and IL-8. In addition, MIF has also been shown to counter-regulate the

immunosuppressive effects of glucocorticoids (Calandra and Roger 2003). MIF promotes cell proliferation as well as regulates glucocorticoid action through sustained phosphorylation and activation of MAPK1/MAPK3 (Mitchell et al. 1999). MIF-mediated activation of PI3K-AKT cascade also contributes to the pro-survival and anti-apoptotic effects of MIF (Lue et al. 2007). MIF has been implicated in the pathogenesis of several acute and chronic inflammatory diseases including sepsis (Calandra et al. 2000; Lehmann et al. 2001), asthma (Yamaguchi et al. 2000), acute respiratory distress syndrome (Lai et al. 2003) and atherosclerosis; autoimmune diseases such as systemic lupus erythematosus (Burger-Kentischer et al. 2002) and rheumatoid arthritis (Leech et al. 1999); metabolic disorders such as type 2 diabetes and obesity (Finucane et al. 2012), and cancer (Kindt et al. 2013; Zhang et al. 2013; He et al. 2006; Funamizu et al. 2012; He et al. 2009; Hagemann et al. 2007; Meyer-Siegler et al. 2007; Subbannayya et al. 2015).

The molecular mechanisms of MIF signaling have been investigated to a considerable extent. However, a detailed documentation of the signaling events downstream of MIF is lacking. A centralized resource that provides a detailed documentation of signaling events pertaining to MIF as well as a depiction of these reactions in a pathway map is desired in the public domain. In order to achieve this, the molecular reactions reported downstream of MIF induction was curated from literature and submitted to NetPath (<http://www.netpath.org>) (Kandasamy et al. 2010). Several such ligand-receptor signaling pathways including fibroblast growth factor-1 (Raju et al. 2014), corticotropin releasing hormone (Subbannayya et al. 2013), brain-derived neurotrophic factor (Sandhya et al. 2013), Oncostatin M (Dey et al. 2013), prolactin (Radhakrishnan et al. 2012), follicle stimulating hormone (Telikicherla et al. 2011), leptin (Nanjappa et al. 2011), have been developed by our group and submitted to NetPath. Here, the generation of an integrated pathway map of MIF signaling by manual curation has been described.

Materials and methods

Annotation of MIF signaling events

A survey of literature was done on PubMed using the search terms – ‘(“Macrophage migration inhibitory factor” OR MIF)’ to identify scientific literature pertaining to MIF signaling pathway. The relevant signaling pathway information obtained from these scientific literatures was manually entered into a web-based pathway data assimilation tool called PathBuilder (Kandasamy et al. 2009). Molecular reactions stimulated by MIF were considered for curation. The molecular reactions chosen to be recorded can be categorized into protein-protein interactions (PPIs), post-translational

modifications (PTMs), protein translocation events, activation/inhibition of proteins and transcriptional regulation of genes and their regulators. The NetPath annotation criteria for manual curation of these reactions have been as described previously (Nanjappa et al. 2011; Radhakrishnan et al. 2012; Raju et al. 2011a). Information pertaining to the different categories of molecular events was captured from research articles studying human and mammalian cells/cell lines. Data specific to each molecular event including type of experiment, source of the protein, species of the cells/cell lines used in the experiment, PTM dependence of the event, subcellular localization of the proteins and PubMed identifiers of the annotated research article have been provided. In addition, a brief textual description for each reaction has been provided in the comments section.

Visualization of MIF signaling pathway

A pictorial representation of the curated pathway reactions was developed using PathVisio (van Iersel et al. 2008). The spatial arrangement of the molecules in the pathway map has been based on the information obtained from, i) inhibitor-based assays; ii) mutation-based assays; iii) knockout studies; iv) canonical pathways; and v) review articles. A set of stringent criteria was applied to obtain a subset of pathway reactions for MIF signaling assimilated in NetPath as described previously by our group (Raju et al. 2011b). A simplified version of the map has also been represented using these confident set of reactions and has been provided in the NetSlim resource (<http://www.netpath.org/netslim>) (Raju et al. 2011b).

Results and discussion

We have screened over 4000 research articles until June, 2015 and documented reactions induced by MIF from 95 articles. This cataloging effort of MIF signaling pathway has yielded 68 molecules found to be involved in 24 PPIs, 44 PTMs, 11 translocation events, 5 activation and 3 inhibition events. Of the 24 PPIs, 22 were direct type of interactions and 2 were found to form a complex. The PTMs annotated include phosphorylation and dephosphorylation. The site and residue information for PTMs of 32 proteins were annotated. The upstream enzyme for 3 PTMs was identified from the research articles. In addition, 65 genes were found to be differentially regulated at the mRNA level on MIF induction. Of these 65 genes, 56 genes were cataloged to be upregulated and 9 genes to be downregulated. The transcriptional regulators were obtained from literature for one of these genes. The reactions annotated for the MIF pathway have been reviewed internally as well as by a Pathway Authority (SS, co-author in this manuscript). A total of 49 pathway reactions have been submitted to Human Protein Reference Database (HPRD) (Prasad et al. 2009; Muthusamy et al. 2013). MIF signaling pathway is freely available in NetPath (http://www.netpath.org/pathways?path_id=NetPath_165).

The MIF pathway page in NetPath provides a short description of the pathway; the pathway statistics as well as the molecules involved in the pathway reactions and transcriptionally regulated genes. Each molecule is linked to its respective NetPath molecule page which provides information pertaining to the molecule including its gene symbol,

Fig. 1 Schematic representation of MIF signaling pathway - This map represents the NetPath reactions of MIF signaling pathway. The different types of reactions are distinguished by colors as described in the legend

accession number, alternate names, its association with other NetPath pathways and its participation in molecular reactions. The molecule page also provides external links to other databases including HPRD (Prasad et al. 2009; Muthusamy et al. 2013), Entrez gene (Maglott et al. 2011), OMIM (Hamosh et al. 2005) and Swiss-Prot (Boeckmann et al. 2003). The MIF pathway data from NetPath and NetSlim can be downloaded in different standard data exchange formats including SBML level 2.1 (Hucka et al. 2003), PSI-MI version 2.5 (Hermjakob et al. 2004) and BioPAX level 3.0 (Demir et al. 2010). The gene regulation information is available in tab-delimited and Microsoft Excel formats.

The molecular events annotated for the MIF signaling pathway in NetPath have been graphically depicted using the PathVisio tool as represented in Fig. 1. In the pathway map of MIF signaling each node represents a molecule as linked to its corresponding molecule page in NetPath and each reaction represented by an edge is linked to PubMed identifiers. Solid edges indicate direct reactions and dashed edges for indirect reactions. PPIs, enzyme-catalysis-reactions, translocation, and activation/inhibition events have been differentiated through depiction using different colors as shown in the legend. On applying the NetSlim criteria to the NetPath curated reactions of MIF signaling pathway, 42 molecules involved in 57 reactions were obtained. These confident set of reactions were used to generate the NetSlim pathway map which can be accessed at http://www.netpath.org/netslim/MIF_pathway.html. An interactive pathway map can be visualized by clicking on ‘map with citations’.

MIF has been shown to have a role as a therapeutic target in various conditions including inflammatory diseases, autoimmune diseases and cancers. Several studies have investigated the mechanism of action of MIF to a considerable extent. A freely available integrated pathway map of MIF signaling will facilitate further molecular discoveries in this signaling. It will also aid in identification of candidate biomarkers for diagnosis as well as to act as a therapeutic target for several disorders. We encourage the scientific community to give their valuable suggestions and critical comments to improve the quality and display of information provided in NetPath through <http://www.netpath.org/comments>

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Compliance with ethical standards

Conflict of interest No potential conflicts of interest were declared.

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