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Review article

Pathogenic contribution of the Macrophage migration inhibitory factor family to major depressive disorder and emerging tailored therapeutic approaches

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ABSTRACT

Background: Immunoinflammatory disorders are often accompanied by depression. Here, we review the available preclinical and clinical studies suggesting a role for the pro-inflammatory cytokine Macrophage migration inhibitory factor (MIF) and the second member of the MIF family, D-dopachrome tautomerase (D-DT; DDT), in the pathogenesis of Major Depressive Disorders (MDD).

Methods: We prepared a narrative review from a search on PubMed of studies pertaining to MDD and MIF, as for October 2019. Both humans and animal studies haves been considered.

Results: Preclinical data show conflicting results on the role of endogenous MIF and DDT in depression. In contrast, several human studies show that circulating MIF levels tend to increase during the course of MDD. Higher levels of inflammatory biomarkers have also been associated with poorer responses to antidepressants and the levels of MIF significantly decrease after treatment, despite this may not be necessarily associated to an improvement in psychiatric symptoms.

Limitations: This is a narrative and not a systematic review of the literature on the involvement of MIF in MDD. We have highlighted studies performed in humans and in animal models, irrespective of population size and methodological approach.

Conclusions: This review highlights a role of MIF, and possibly DDT, in the pathogenesis of MDD. Whilst studies in animal models are discordant, the studies in patients with MDD convergently suggest that MIF plays a role in induction and maintenance of the disease. Additional studies are also needed on DDT that often displays synergistic function with MIF and their receptors.

1. Introduction

1.1. Major depressive disorder (MDD)

MDD is a common and sometimes fatal disorder that has been identified by the World Health Organization as a leading cause of disability (Moussavi et al., 2007). It is estimated that ~20% of people worldwide is going to experience a major depressive episode during their lifetime (Kessler et al., 2005). Although standard of care (SOC) treatment with antidepressants may successfully treat the majority of depressed patients, ≈50% respond poorly to current treatment, and alternative or synergistic therapeutic strategies are required for this subset of patients (Ignácio et al., 2016).

The drugs used in SOC are designed to counteract the deregulated activity of biogenic amines in the brain's limbic and cortical circuits commonly considered the primary cause of the main symptoms of depression. Hence, new therapeutic approaches are warranted for the treatment of MDD that may offer a more personalized approach to the underlying cause of the disease and cure both symptoms and dysregulated pathogenetic pathways that control disease development and maintenance.

During the last several years, the convergent observations that diseases characterized by chronic inflammation such as certain cancers, type 2 diabetes, psoriasis and arthritis are accompanied by depression

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has suggested a role of immunoinflammatory responses in the pathogenesis of MDD. Abnormalities of the immune system in depressed patients have been reported during the last several years. While the initial studies suggested reduced immune responses in depressed patients, it has then been shown that upregulated immune responses might play a pathogenetic role in major depression (Raison et al., 2006).

Along this line of research, the possible role of soluble polypeptides and glycoproteins, termed cytokines, in the pathogenesis of MDD has been recently investigated. The contribution of cytokines to MDD was empirically suggested by the observation that patients treated with recombinant cytokines such as interleukin (IL)-2 or interferon (IFN)-alpha often developed neuropsychiatric symptoms, some of them characteristic of MDD (Myint et al., 2009; Su et al., 2019). While, in some cases, the symptoms ceased at interruption of treatment, other patients suffered from long-lasting cognitive impairment after medication interruption. In preclinical studies, other cytokines, for example IL-1 and IL-6, may induce sickness behavior. It is also known that a challenge with lipopolysaccharide (LPS) that induces massive release of cytokines into the bloodstream provokes sickness behaviour and depressive-like behaviour (Farooq et al., 2017).

It has also been shown that IL-1β stimulates the hypothalamic-pituitary-adrenocortical (HPA) axis, that is frequently upregulated in MDD (Simões et al., 2019). Increased levels of cortisol are frequently found in MDD, and interventions aimed at reducing glucocorticoid levels may have beneficial effects on these conditions (Farooq et al., 2017). Recent studies have shown that several cytokines are increased during MDD and that the elaboration of these cytokines can be reduced in response to standard antidepressive treatment (Köhler et al., 2017a,b). The increase is not limited to proinflammatory T helper (Th) 1 and Th17 cytokines but also include anti-inflammatory Th2 cytokines, such as IL-10 and IL-13 (Myint et al., 2005).

This has led to the so-called cytokine hypothesis of MDD that postulates that dysregulated production of proinflammatory cytokines including, among the others, tumor-necrosis factor (TNF)-α, IL-1β, IL-6, IL-12, IL-17, IL-18 and may contribute to the initiation and maintenance of MDD through multiple mechanistic biological pathways (Lotrich, 2012).

Subsequently, an attempt of regulatory feedback is activated by the compensatory immune-regulatory reflex system (CIRS), that determines an upregulated production of Th2/Th3 anti-inflammatory cytokines, such as IL-10 and IL-13 and transforming growth-factor (TGF)-β, and other endogenous inhibitors of cytokines, e.g. interleukin-1 receptor antagonist (sIL-1RA), soluble IL-2 receptor (sIL-2R), counterbalances the ongoing pathogenic inflammation driven from the proinflammatory cytokines (Gérard et al., 1993; Maes and Carvalho, 2018; Nicoletti et al., 1997).

The soundness of this concept was highlighted by a meta-analysis conducted on 82 studies that revealed increased blood concentrations of IL-6, TNFα, IL-10, the soluble IL-2 receptor, C−C chemokine ligand 2 (CCL2), IL-13, IL-18, IL-12, sIL-1RA, and soluble TNF receptor 2, in MDD patients vs. healthy controls (HCs). This study also reported that IFN-γ levels were lower in MDD and levels of IL-1β, IL-2, IL-4, IL-8, the soluble IL-6 receptor (sIL-6R), IL-5, IL-17, CCL-3 and TGF-β were not significantly altered in individuals with MDD compared to HCs (Köhler et al., 2017a,b).

Moreover, a recent meta-analysis study showed that antidepressant drug treatment significantly decreased peripheral levels of IL-6, TNFα, IL-10, and CCL2, hence highlighting an immunopharmacological effect of at least some antidepressive drugs (Köhler et al., 2017a,b).

Several different and often cytokine-specific mechanisms have been proposed to explain the putative role of cytokines in the pathogenesis of MDD (Fig. 1). For example, a recent hypothesis suggests that the proinflammatory cytokines may contribute to MDD development by activating the enzyme indoleamine 2,3-dioxygenase, that metabolizes tryptophan into the neurotoxic compounds,3-hydroxykyurenin and quinolinic acid. In turn, this would lead to depletion of local stores of tryptophan, necessary for the synthesis of serotonin. Accordingly, indoleamine 2,3-dioxygenase 1 (IDO1) induces depression-like behavior (Lawson et al., 2013).

The inflammasome is a constituent of innate immunity (Yang and Chiang, 2015). This molecular complex is activated by both endogenous (e.g. urate crystals) and exogenous (e.g. LPS) stimuli releasing, among other factors, IL-1β and IL-18. It has also attracted attention as a possible pathogenetic contributor to MDD (Bhattacharya and Jones, 2018).

Although not included in the meta-analysis by Köhler and coworkers, several recent studies indicate that another cytokine, macrophage migration inhibitory factor (MIF), exerts peculiar biological features that make it a potential pathogenetic mediator of MDD and, possibly, a therapeutic target (Köhler et al., 2017a,b).

1.2. Macrophage migration inhibitory factor: a potential key cytokine in MDD

1.2.1. The MIF family of cytokines

MIF was first discovered in guinea pigs in 1963 and in humans in 1971/72 as a T-lymphocyte cytokine released in delayed-type hypersensitivity reactions; its name derived from its property to impair the random migration of macrophages (Rocklin et al., 1980).

Since then, MIF has been studied as an immunoneuroendocrine mediator released by other cell types, including macrophages, monocytes, pituitary cells and vascular endothelial cells (Kasama et al., 2010). MIF is a pleiotropic protein entailing the biological properties of both a cytokine and a hormone. MIF also acts as a cytosolic chaperone protein and has enzymatic functions, including D-dopachrome, phenylpyruvate tautomerase, and thiol-protein oxidoreductase activities.

Upon binding of MIF to the CD74 receptor, the glycoprotein CD44 is recruited, with the subsequent activation of intracellular signaling pathways, such as the mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK), Src, phosphoinositide 3-kinase (PI3K)/Akt, and nuclear factor (NF)-κB pathways. Also, MIF signaling is activated following the binding of the chemokine receptors, CXCR2, CXCR4, and CXCR7 (Jankauskas et al., 2019) (Fig. 2). A second member of the MIF family, the DDT gene, also known as MIF-2, has been recently characterized that share most, but not all, biological functions of MIF (Fagone et al., 2018; Mangano et al., 2018; Presti et al., 2018). In humans, the DDT gene is located approximately 80 kb from the MIF gene on chromosome 22. Similarly to MIF, DDT is composed of three exons and two introns and in there are predicted binding sites for both SP-1 and CREB in its promoter. The DDT protein shows a 35% sequence homology with MIF and catalyzes a similar enzymatic reaction, although the end-products are different (Günther et al., 2019). Merk and collegues have demonstrated that DDT binds CD74 with high affinity, with consequent activation of the ERK1/2 MAP kinase pathway. Also, in mice, during sepsis, the blood levels of D-DT correlate with disease severity and the immunoneutralization of DDT is able to confer protection from lethal endotoxemia (Merk et al., 2011). In mammals, D-DT is constitutively expressed in different tissues, such as the brain, heart, liver, lung, kidney, spleen, testis and ovary. In particular, Honigman and collaborators have observed that DDT is localized to interneurons of the cerebral cortex and hippocampus, as well as in the cerebellum (Honigman et al., 2012).Although most data indicate a proinflammatory role of MIF in several immunoinflammatory and autoimmune conditions including type 1 diabetes, multiple sclerosis and Guillain Barré syndrome and cancers such as glioblastoma, melanoma and neuroblastoma (Benedek et al., 2017; Cavalli et al., 2019a, 2019b; Cvetkovic et al., 2005; Fagone et al., 2018; Leyton-Jaimes et al., 2018; Mangano et al., 2018; Nicoletti et al., 2005; Presti et al., 2018; Soumoy et al., 2019), increasing observations indicate a complex role of MIF in polarization of immune responses that entails activation of both pro and anti-inflammatory effects (Günther et al., 2019).

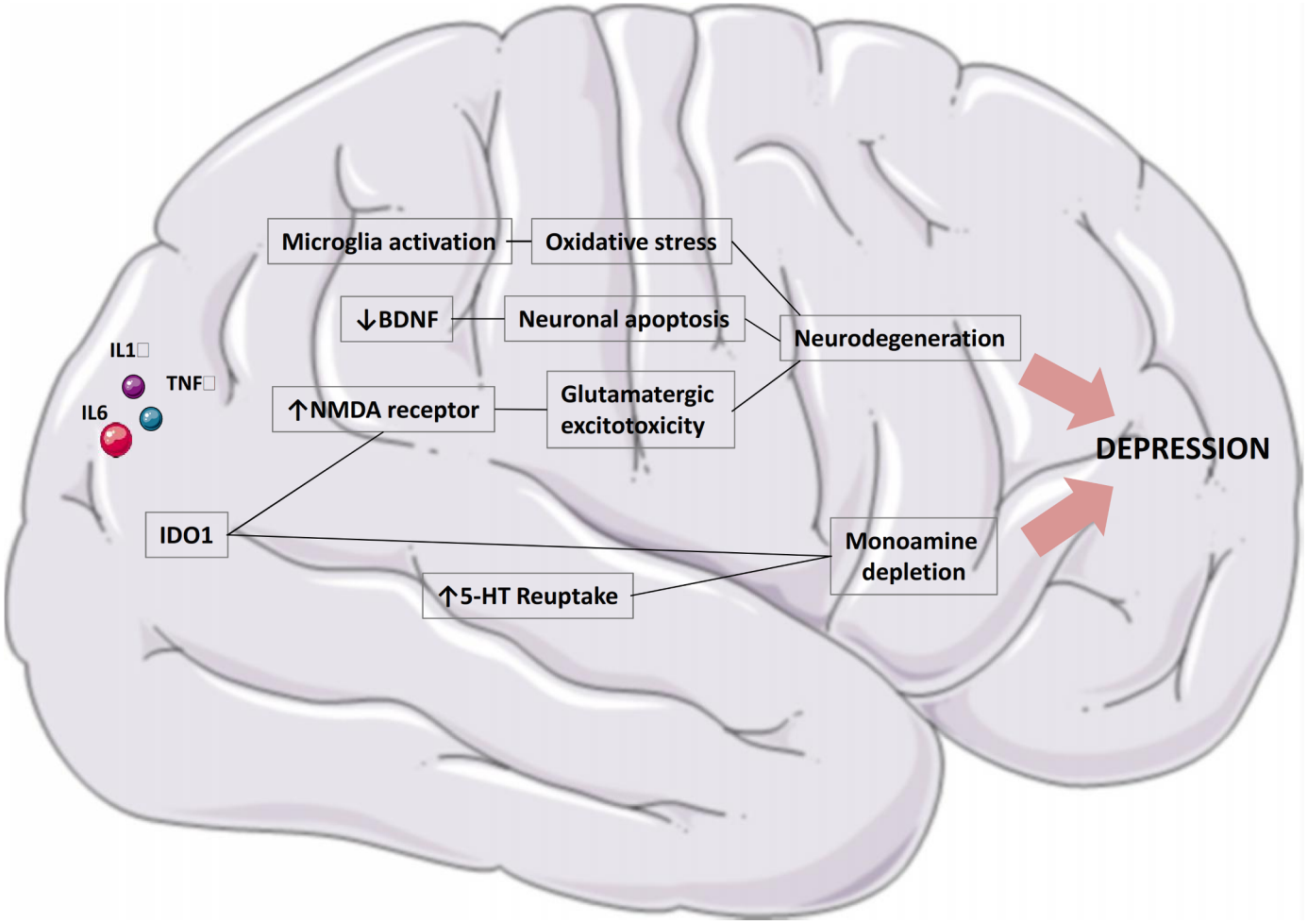

Fig. 1. Role of cytokines and inflammation in the etiopathogenesis of Major Depressive Disorder (MDD). According to the cytokine hypothesis, both internal or external stressors induce the production of pro-inflammatory cytokines, which in turn promote the development of depressive symptoms in susceptible individuals. The inflammatory reaction activates the indoleamine-2,3-dioxygenase (IDO) enzyme which catalyzes the metabolism of the 5-HT precursor, tryptophan, to kynurenine, inhibiting the synthesis of 5-HT. Also, the pro-inflammatory cytokines reduce neuroplasticity by increasing the levels of quinolinic acid, a strong agonist of the N-methyl-D-aspartate (NMDA) receptor. Finally, cytokines decrease the levels of BDNF, that regulates synaptic function in the central nervous system, leading to neurodegeneration and consequently, depression. BDNF: Brain-derived neurotrophic factor; IDO1: Indoleamine 2,3-dioxygenase-1; NMDA: N-Methyl-D-aspartic acid; 5-HT: 5-hydroxytryptamine.

In fact, MIF may trigger the secretion of both Th1/17 and Th2 cytokines by T-lymphocytes, thus suggesting that it does not exert a unique clear role in T cell polarization. Moreover, MIF and D-DT can exert anti-inflammatory properties, through the activation of AMP kinase (AMPK) (Günther et al., 2019).

MIF also activates the inflammasome that, as mentioned above, is an increasingly recognized player in the pathogenesis of MDD and also a potential therapeutic target (Harris et al., 2019; Lang et al., 2018; Shin et al., 2019). MIF may also play a pathogenic role in MDD by upregulating production of cytokines, including IL-1β and TNFα (Günther et al., 2019) that are known activators of IFN??-independent pathways of IDO. This leads to upregulated expression of kynurenines (Campbell et al., 2014). Both IDO and kynurenins are attracting attention as key mediators of CNS disorders including MDD (Campbell et al., 2014). It should be noted, however, that MIF could play a protective role in MDD by upregulating the Pi3k/Akt/mTOR pathway (Oliveira et al., 2014), that seems to play a beneficial and disease limiting role in MDD (Ignácio et al., 2016).

In addition to its role in immunoinflammatory reactions, MIF is also a hormone, that is released by the anterior pituitary and adrenal gland, following HPA activation. Thus, the regulation of MIF production from glucocorticoids is biphasic and concentration-dependent with “low” levels promoting MIF release from T cells and macrophages, and ”high” levels suppressing MIF secretion (Aeberli et al., 2006). On the other hand, once it is released, MIF counter-regulates the suppressive effects of glucocorticoids on target immunoinflammatory cells and through this porperty it may be responsible of induction of steroid resistance (Calandra and Bucala, 1997; Wang et al., 2012).

1.2.2. MIF and central nervous system

MIF protein has been detected by immunohistochemistry in the subependymal astrocytes, CA3/CA4 pyramidal cells of the hippocampus and in granule cells of the dentate gyrus, of the bovine brain (Nishibori et al., 1996). MIF was also expressed in rat brains in the choroid plexus epithelia, ventricular ependymal cells and in astrocytes (Ogata et al., 1998). MIF transcripts were also confirmed in astrocytes and neurons (Ogata et al., 1998). Furthermore, MIF expression has been observed in neurons of the cortex and the subgranular zone of the hippocampus of rat brains, as well as in astrocytes and the hypothalamus, cerebellum and pons (Bacher et al., 1998; Conboy et al., 2011). Interestingly and important for neurogenesis, these areas have both proliferating and maturing cell populations. There is also a significant colocalization with glucocorticoid activation. High levels of MIF have been found in all regions of the human brain (Matsunaga et al., 1999).

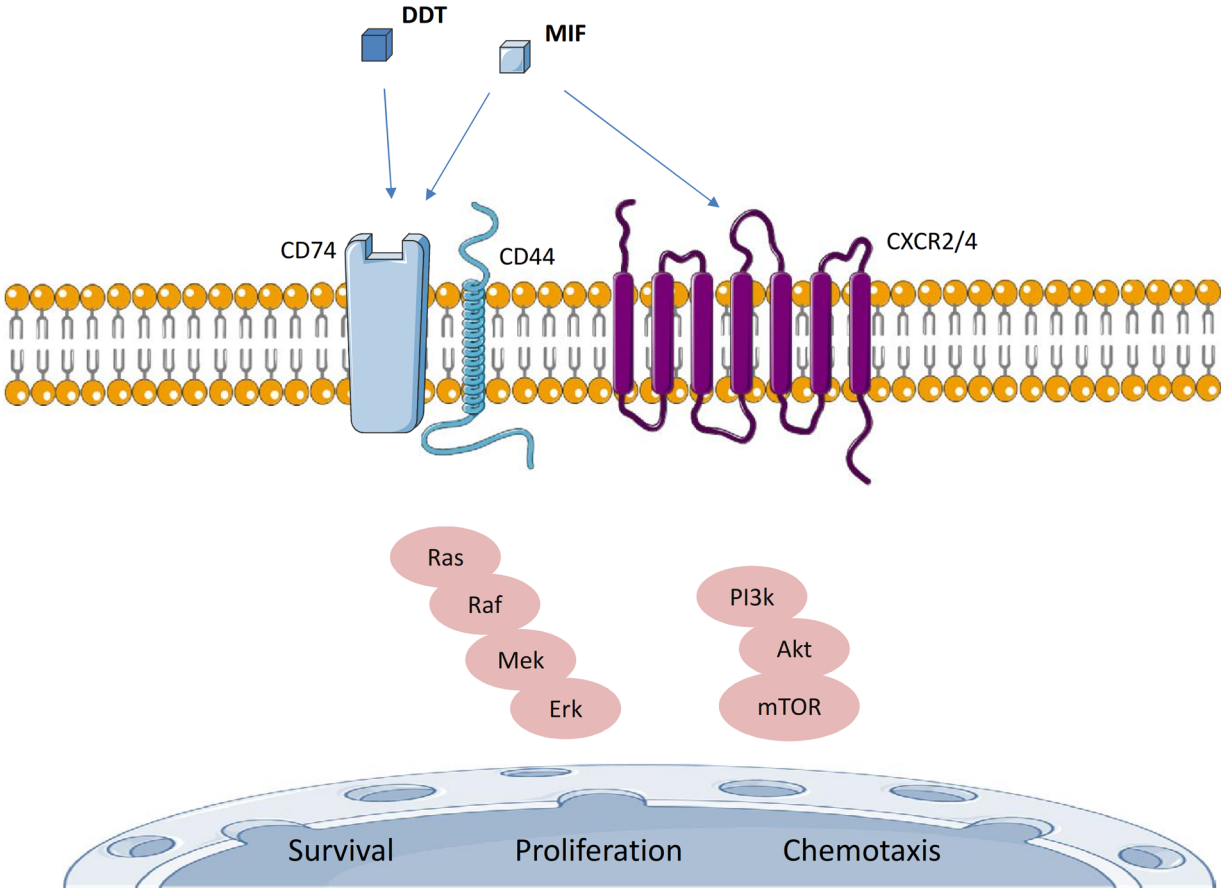

Fig. 2. Macrophage Migration Inhibitor Factor (MIF) signaling. Upon binding of MIF to the CD74 receptor, the glycoprotein CD44 is recruited, with the subsequent activation of intracellular signaling pathways, such as the mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK), Src, phosphoinositide 3-kinase (PI3K)/Akt, and nuclear factor (NF)-κB pathways. Also, MIF signaling is activated following the binding of the chemokine receptors, CXCR2, CXCR4, and CXCR7.

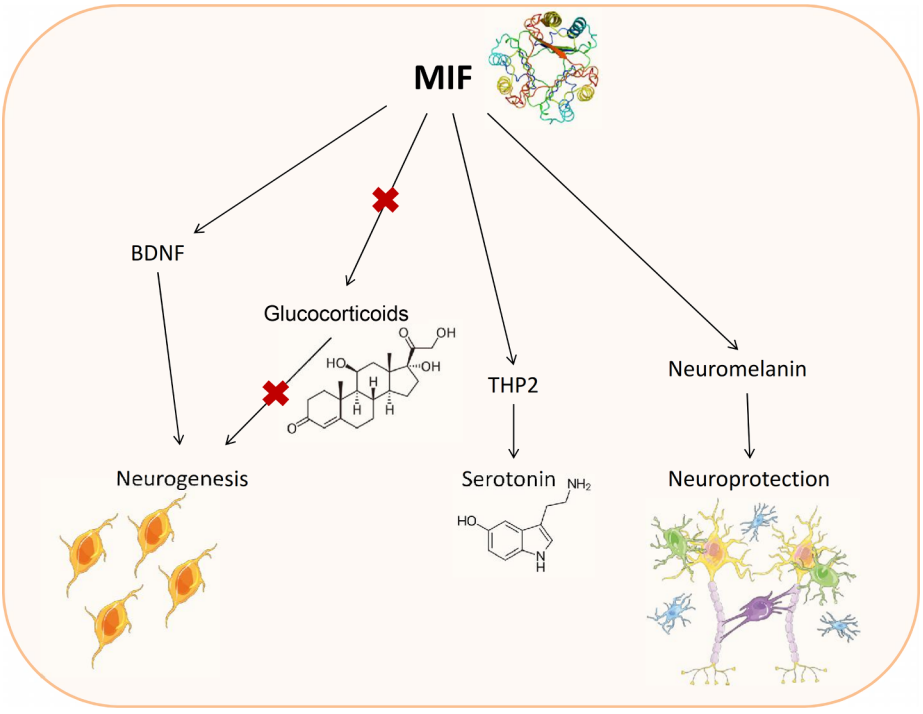

Fig. 3. Role of Macrophage Migration Inhibitory Factor (MIF) in Major Depressive Disorders (MDD). MIF has been shown to play a significant role in the pathobiology of depression. MIF induces the upregulation of both brain-derived neurotrophic factor (BDNF) and tryptophan hydroxylase-2 (Tph2), a rate-limiting enzyme in production of serotonin. Also, MIF has been proposed to catalyze the isomerization of reactive catecholamine metabolites to neuromelanin precursors. On the other hand, MIF counteracts the activity of glucocorticoids, with consequent disruption of the hypothalamic-pituitary-adrenal (HPA) axis. BDNF: Brain-derived neurotrophic factor; THP2: Tryptophan hydroxylase-2.

Notably, MIF levels in the CNS remain largely unaltered throughout the life-span, in accordance to the hypothesis that MIF may exert an homeostatic role by promoting the isomerization of catecholamine metabolites to neuromelanin precursors (Solano et al., 2000). Neuromelanin has been shown to be neuroprotective in the pathobiology of Parkinson's disease due to its role as a scavenger and sink for toxic metabolites (RAO et al., 2006).

MIF has putative roles in several inflammatory and neoplastic conditions of both the central and peripheral nervous system (CNS), including multiple sclerosis and Guillain Barre' syndrome (Günther et al., 2019) and cerebral ischemia-reperfusion injury (Chen et al., 2012; Kithcart et al., 2010). MIF has also been implicated in tumor growth in the CNS (Bloom and Al-Abed, 2014; Savaskan et al., 2012). In addition, MIF has been studied for its role in neurodegenerative, vascular and traumatic disorders of the nervous system (Leyton-Jaimes et al., 2018) Thus, MIF plays a complex and still not completely identified role in disorders such as Alzheimer's disease (Oikonomidi et al., 2017), autism-spectrum disorders (Ning et al., 2019) and spinal cord injury where it contributes to the severity of the injured area (Su et al., 2017; Zhou et al., 2018) while, on the other hand, exerting a beneficial role in an mouse model of amyotrophic lateral sclerosis by reducing aggregated misfolded SOD1 (Leyton-Jaimes et al., 2016).

On the other hand, in spite of several preclinical and clinical studies the role of MIF in the pathogenesis of MDD has not been clearly defined and theories on its role as pro and anti-depressants molecule have been advanced.

In the remainder of this review we will analyze the available preclinical and clinical studies of MIF in MDD and the single preclinical study suggesting a pro-depressant role of DDT (Fig. 3). We will also discuss putative MIF-, and eventually DDT, suppressive approaches as for the treatment of MDD.

2. Methods

For this narrative review, studies were identified by interrogating PubMed, from inception through October 2019. Articles chosen for this review were published in English and could include humans or animals data. The PubMed search was conducted using combinations of the following terms: major depressive disorder, MIF, DDT, cytokines, depression, antidepressant response.

3. Results

3.1. Anti-depressant and pro-depressant effects of endogenous MIF and DDT: preclinical models

The role for MIF in cycling cells of the dentate gyrus was studied by using MIF KO mice and ISO1, a specific inhibitor of MIF. MIF-KO mice exhibited augmented depression-like behaviour and anxiety, as well as reduced hippocampus-dependent memory. This indicates that MIF may be implicated in the proliferation of hippocampal cells both in basal condition and upon antidepressant stimulation. Thus, selective loss of MIF results in a behavioural phenotype that, to a large extent, corresponds with alterations predicted to arise from reduced hippocampal neurogenesis (Conboy et al., 2011). These data were later supported by the observation that the antidepressant effect of voluntary exercise may be mediated by MIF (Moon et al., 2012). Moreover, in vitro, MIF induces in vitro the expression of tryptophan hydroxylase 2 (Tph2) and brain-derived neurotrophic factor (BDNF), in a manner similar to that observed during both exercise and electroconvulsive seizure in vivo (Moon et al., 2012). This increase in Tph2 was associated to augmented levels of serotonin, and was mediated by the CD74 receptor and the ERK1/2 pathway. Finally, administration of recombinant MIF produced antidepressant-like behavior in rats in the forced swim test (Moon et al., 2012). Another study has evaluated the histopathology and expression of BDNF, MIF, vascular endothelial growth factor (VEGF) and IL-6 in the dentate gyrus (DG), medial prefrontal cortex (mPFC) and cerebellum of Wistar rats during depression and after practicing voluntary running. While, during depression, the content of these molecules was significantly decreased in all examined areas, the running, significantly increased them in all areas. In particular, MIF and VEGF were detected in the neurons in DG, mPFC and in Purkinje cells, while IL-6 was expressed in neurons of the DG, in the neuropil of mPFC and in Purkinje cells (Algaidi et al., 2019).

In contrast to these findings, Bay-Richter C and colleagues have demonstrated that both male and female MIF KO mice underwent reduced depressive-like behaviors, as determined by the forced swim test (Bay-Richter et al., 2015). In the sucrose preference test, there was a sex-specific difference, as male MIF KO mice had reduced anhedonia-like behaviours, while female KO mice showed increased anhedonia-like behaviour. The authors suggested that this might have been due to the higher levels of corticosterone found in female MIF KO mice as compared to male mice. They also found that the pro-depressant effects of MIF might be mediated by IFN-γ, as IFN-γ concentrations were reduced while dopamine metabolism augmented, in MIF KO mice. Decreased brain IFN-γ levels were accompanied to higher dopamine levels in the striatum and, in turn, to a reduced depressive-like behaviour (Bay-Richter et al., 2015). Further support for a pro-depressant role of MIF was provided by Gellen et al. who (Gellén et al., 2017), observed that in the prefrontal cortex of neonatally clomipramine-treated adult rats, the proteins correlates with behavioural abnormalities. The identified proteins related to several biological functions, such as inflammation, transcription, cell metabolism and cytoskeleton organization. Among the altered proteins, the level of MIF showed the largest alteration. Immunohistochemistry analysis also showed a widespread distribution of MIF, predominantly located in astrocytes of the rat forebrain (Gellén et al., 2017).

On the other hand, data on the possible involvement of DDT in MDD are still scarce. To the best of our knowledge, there is only one published study on a murine model of depression, where significantly lower levels of DDT were found in both the ventral and dorsal Dentate Gyrus upon treatment of mice with the antidepressant fluoxetine (Samuels et al., 2014). Interestingly, no modulation was observed in mice not responding to fluoxetine (Samuels et al., 2014), suggesting that DDT may exert pro-depressant effects and its downregulation could entail response to treatment. Most importantly, no significant modulation of MIF was observed, supporting the notion that MIF and DDT may have divergent roles in this setting.

3.2. Clinical studies

3.2.1. Genetic polymorphism

It is known that the −173*C allele and CATT7 repeat are variants of the *MIF* gene associated with greater MIF expression (Radstake et al., 2005).

However, the association of MIF variant with MDD has been little studied and it may represent an important area of research. So far, one study carried out on Iranian type 2 diabetes patients, has demonstrated that MIF 173 G > C polimorphism was associated with depressive disorders (Hamidi et al., 2019). In another study it was shown that young people carrying the MIF-173*C and CATT7 alleles displayed attenuated cortisol reactivity, when compared to non-carriers and that subjects with the CATT7-173*C haplotype had lower cortisol reactivity to the stressor compared to those without this haplotype. Also, lower self-reported anxiety ratings following the stressor were reported by individuals carrying the CATT5-173*C and CATT6-173*C haplotypes. These data seem to support a role for MIF in the neuroendocrine response to stress and the pathological pathways involved in stress-related disorders (Lipschutz et al., 2018).

In contrast, MIF promoter polymorphisms and haplotype analysis in Japanese suicide victims did not show significant differences between

the suicide completers and the controls (Shimmyo et al., 2017).

3.2.2. Peripheral levels of MIF in MDD

Several studies concordantly show that MIF levels in the circulation tends to increase during the course of MDD. Edwards and coworkers (Edwards et al., 2010, 2010) studied the association between MIF, loneliness and depressive symptoms as well as the relation between circulating MIF concentrations and the HPA, i.e., diurnal cortisol levels and cortisol response to acute stress. University students, in the upper or lower quintile on the Beck Depression Inventory or UCLA loneliness scale were recruited and plasma MIF and salivary cortisol determined following a public speaking task. MIF levels resulted incremented by 40% in the high-depressive symptoms group as compared to the low depressive symptoms group. Also, increased MIF concentrations were associated with lower cortisol response to acute stress and reduced diurnal morning cortisol values, even after adjustment for depressive symptoms, and demographic, anthropomorphic and behavioural factors. Depressive symptoms were likewise associated with lower morning cortisol, but this association was not statistically significant after adjustment for MIF levels (Edwards et al., 2010). Augmented blood levels of MIF in patients with MDD were also found from Musil and coworkers (Musil et al., 2011).

Adding strength to the possible pro-depressant role of MIF in human MDD, it is also the finding that high circulating MIF levels at admission were associated with increased risk of post-stroke depression three months after an ischemic stroke, suggesting that monitoring circulating MIF levels may be used to identify patients at risk of developing post-stroke depression (PSD), for early prevention strategies in these patients (Xu et al., 2018).

3.2.3. MIF as biomarker and theragnostics

Higher blood levels of inflammatory biomarkers have been associated with scarne responses to antidepressants (Cattaneo et al., 2016). This observation may have diagnostic and therapeutic implications. It has, for example, been shown that is possible to discriminate different responses of MDD patients to nortriptyline vs escitalopram on the basis of blood C-reactive protein (CRP) values (Uher et al., 2014). In a systematic review on potential inflammatory markers and treatment outcome in treatment resistant depression, Yang and collaborators found that higher baseline IL-6 or CRP in blood predicted better response to drug treatment, while they found no evidence for the predictive value of other inflammatory mediators, including TNF-α, IFN-γ (Yang et al., 2019). CRP, however, is a common and final marker of inflammation unable to discriminate between different molecular pathways of immune-inflammation, and much effort has therefore been directed to identify biomarkers such as MIF that could predict and tailor therapeutic approaches.

Along this line of research, and as a part of the Genome-based Therapeutic Drugs for Depression (GENDEP) study, the authors analyzed the white blood cells transcriptional levels of genes belonging to glucocorticoid receptor (GR) functions *FKBP* (FK506 binding protein) −4, *FKBP-5*, and *GR*, and inflammation *IL-1α*,: *IL-1β, IL-4, IL-6, IL-7, IL-8, IL-10, MIF, TNFα, BDNF, p11* and *VGF*, in healthy controls and depressed patients, before and after 8 weeks of treatment with escitalopram or nortriptyline. MIF was the cytokine with the highest baseline mRNA levels (+48%) among non-responders followed by TNF-α (+39%) and IL-1β (33%). Antidepressant treatment determined a reduction in the levels of *IL-1β* (−6%) and *MIF* (−24%), and an increase in the levels of *GR* (+5%) and *p11* (+8%), although these changes were not associated with treatment response (Cattaneoet al., 2013). On the other hand, response to the treatment was associated with a reduction in the levels of *IL-6* (−9%) and of *FKBP5* (−11%), and with an increase in the levels of *BDNF* (+48%) and *VGF* (+20%), thus implying that response was associated with changes in genes that did not predict the response at baseline. These findings suggest that, although higher levels of proinflammatory cytokines are able to predict unresponsiveness of patients to antidepressant drugs, changes in inflammatory cytokines' patterns may vary. On the contrary, modulation of the GR complex and of neuroplasticity is needed to observe a therapeutic antidepressant effect (Cattaneo et al., 2013).

In another study, that used the backward Wald logistic regression model, MIF and IL-1β resulted strongly associated with treatment response. Moreover, the power of the model increased when IL-1β, but not TNF-alpha,was evaluated together with MIF. Of note, the ORs were similar when the response prediction to escitalopram and to nortriptyline, were evaluated separately (Cattaneo et al., 2016).

Furthermore, MIF and IL-1β were reciprocally regulated, as the increased activation of one cytokine had downstream effects on the other. MIF interacted mainly with ubiquitin C via matrix metalloproteinase 9, which regulates neurogenesis, neuroplasticity, and cell proliferation, like endothelial growth factor, Notch, and SMAD proteins (Anacker et al., 2013; Marschallinger et al., 2014). On the other hand, the neighbor targets of IL-1β were mainly proteins with inflammatory properties, such as IL-6 and CRP, Toll-like receptors, caspases, and nuclear factor κ-light-chain-enhancer of activated B cells. Interestingly, all of these genes are related to the inflammasome complex or are mediators of oxidative stress, well known causes of neurodegeneration (Cattaneoet al., 2016; Radi et al., 2014; Wang et al., 2018). In agreement with these concepts, a clinical study demonstrated an association of the effects of lamotrigine on cognitive functions with reduction in blood levels of MIF (and IL-1β and IL-6) in patients with depression or recurrent bipolar disorder (Shi et al., 2018).

However, the administration of the COX-2 inhibitor celecoxib as add-on therapy in patients with MDD treated with reboxetine resulted in a significant reduction of Hamilton Depression Scale scores compared to placebo, and this effect was unrelated to modifications of the levels of augmented MIF or decreased TGF-β. Limitations of this study were the small sample population and lack of functional evaluation of the HPA axis (Musil et al., 2011).

3.2.4. MIF as a therapeutic target in MDD

While conflicting results have been reported on the role of MIF in rodent models of depression, converging evidence indicates that it may play a pathogenetic role in human MDD. However, much remains to be studied to conclude that MIF may function as a biomarker predictive of therapeutic response and a therapeutic target.

The role of the second member of the MIF family, DDT or MIF-2 in MDD also remains to be studied. As MIF and DDT often exert synergistic actions (Günther et al., 2019), an association could be dismantled if the response to antidepressives is studied in connection with simultaneous changes in MIF and DDT levels. Several variables, including sex and BMI, need also to be carefully evaluated when considering the role of MIF and DD-T in MDD and their clinical utility as specific antagonists. Benedek et al. have recently demonstrated that DDT and MIF are augmented in male patients with progressive MS (Benedek et al., 2017). In a similar manner careful gender-related evaluation of MIF and DDT in MDD is warranted.

The feasibility and potential beneficial effects of immunomodulatory and anti-inflammatory agents as either add-on or monotherapy for the treatment of MDD has been shown in a recent meta-analysis from randomized clinical trials. The meta-analysis has evaluated non-steroidal antiinflammatory drugs, cytokine inhibitors, statins, minocycline, pioglitazone, and glucocorticoids. It was found that anti-inflammatory agents counteracted depressive symptoms compared to placebo both as add-on in MDD patients and as monotherapy. Indeed, anti-inflammatory add-on therapy improved both response and remission (Köhler-Forsberg et al., 2019).

More specific anti-cytokine therapeutic therapies have already proven effective, as monoclonal antibody (mAb) targeting TNF-α, and the anti-IL-6 receptor antagonist, tocilizumab, showed statistically significant amelioration in depressive symptoms (Kappelmann et al., 2018).

While the several specific chemical and biological antagonists of MIF are discussed in recent reviews by ourselves and others (Günther et al., 2019; Kok et al., 2018), it is worth noticing that multiple small molecules that inhibit the function of MIF by disrupting its tautomerasic activity have been described (Kok et al., 2018). More recently a dual inhibitor of MIF and DDT has also been described (Rajasekaran et al., 2014).

Additionally, the specific small molecule MIF inhibitor, Ibudilast, deserves special attention. Originally developed for the treatment of bronchial asthma, Ibudilast is a nonselective inhibitor of various phosphodiesterases and a non-competitive inhibitor of the p-hydroxyphenylpyruvate tautomerase activity of MIF. The drug is being repurposed as an anti-MIF inhibitor in autoimmune diseases, such as multiple sclerosis (Cho et al., 2010; Fox et al., 2018) The possible use of Ibidulast in mood disorders has been studied recently with positive results in patients with alcohol use disorder (Cummings et al., 2018). Hence, Ibudilast that could be available for immediate use for certain cases of MDD that are resistant to SOC treatment.

Anti-MIF mAb that have been used in Phase I/II studies in cancer patients and patients with systemic lupus could also be considered for immediate use in proof of concept studies in MDD patients. In a similar manner, anti-CD74 mAb that are in Phase II studies in patients with hematological malignancies could also be considered for immediate testing in MDD patients that are resistant to SOC treatment (Berkova et al., 2010).

Biomarker-driven studies might be considered in patients with high circulating levels of MIF and/or IL-1 β as these factors are associated with lack of therapeutic response in MDD (Cattaneo et al., 2016; Colpo et al., 2018).

Specific MIF inhibitors have also become of major interest in the clinical setting of resistant cases of MDD that are treated with SOC and added antipsychotic therapy (Cui et al., 2018). In fact, atypical antipsychotic drugs, such as olanzapine, exhibit adverse metabolic effects including development of insulin resistance. It was indeed found that olanzapine, administered as monotherapy, increased BMI and circulating concentrations of insulin, triglyceride and MIF in schizophrenic patients with normal MIF expression, but not in genotypic low MIF expressers. In agreement with these data, administration of olanzapine to mice increased food intake and hypothalamic MIF production, activating the appetite-related AMP-activated protein kinase and Agouti-related protein pathway. Olanzapine also increased the expression of MIF in the adipose tissue, with consequent reduction in lipolysis and increased lipogenesis. In turn, the higher plasma lipid levels led to fat deposition in the liver and the skeletal muscle, promoting insulin resistance. The authors have also demonstrated that MIF-KO, or the intracerebroventricular injection of neutralizing anti-MIF antibody, protected mice from olanzapine-induced insulin resistance, suggesting the involvement of hypothalamic MIF in metabolic dysfunction (Cui et al., 2018).

These findings reveal the potential value of MIF genotyping and suggest that specific MIF inhibitors may represent a promising class of compounds for reducing the metabolic side effects of atypical antipsychotic therapy in individuals with normal MIF expression.

3.2.5. MIF and psychotherapy

Increasing evidence indicates that psychotherapy exerts beneficial effects in a wide range of psychological disorders including depression (Cuijpers et al., 2019). In addition, psychotherapy is efficacy to reduce depression in patients with a chronic medical conditions, such as cancer (Coyne, 2012). In. Results of systematic review and meta-analysis revealed that cognitive and behavioral interventions can be as effective as antidepressant drugs and more enduring (Hollon et al., 2019, 2005; Thase et al., 1997). In addition, combined antidepressant medication with psychotherapy is more effective for treatment of depression. Although few data are still available on the influence of psychotherapy in the modulation of immunoinflammatory events occurring in MDD, emerging data seems to suggest that psychotherapy may play an immunomodulatory role in MDD For instance, results of a randomized clinical trial demonstrated that two brief cognitive therapy decreased blood concentrations of IL-6 and TNF-α (Moreira et al., 2015). Of particular interest for the present review is the finding that the levels of MIF were significantly reduced in patients with depression, anxiety, or stress and adjustment disorders after 8 weeks of psychotherapeutic intervention (Wang et al., 2018). Nevertheless, MIF reduction was not associated with a progress in psychiatric symptoms. Clearly more studies are needed to prove whether and at which extent psychotherapy may specifically influence MIF, and eventually DDT, leaves in MDD. In this regard, a systematic review and meta-analysis has shown that (O'Toole et al., 2018) psychological interventions was able to temporarily decrease the levels of a non specific pro-inflammatory biomarker such as CRP.

4. Discussion

In this review, we propose a pathogenic role of MIF in the development and maintenance of MDD. This assumption is consistent with clearer and stronger evidences that have been generated primarily in the clinical setting since the first review on MIF in MDD has been published in 2014 and that debated on whether MIF is a pro-depressant or anti-depressant molecule (Bloom and Al-Abed, 2014).

We have discussed above these recent clinical evidences that have been published after the publication of this review and that include: (i) the demonstration that MIF and IL-1β are strongly associated with response to escitalopram (Cattaneo et al., 2016); (ii) the associated effects of lamotrigine on cognitive functions and reduction in blood levels of MIF (and IL-1β and IL-6) in patients with depression or recurrent bipolar disorder (Shi et al., 2018); (iii) the increased blood levels of MIF observed in patients with depression, anxiety, or stress and adjustment disorders and that are reduced after 8 weeks of psychotherapeutic interventions (Wang et al., 2018) and (iv) the finding that high levels of MIF at admission are associated with increased risk of post-stroke depression (Xu et al., 2018).

As regard the potential translation of the experimental evidence implicating MIF in MDD development we hypothesize here for the first time the possible use of the dual orally available PDE and MIF inhibitor, Ibudilast in MDD. This is also supported from the safety and initial efficacy that this drug has shown in patients with alcohol use disorders and multiple sclerosis that may both recognize a pathogenetic role of MIF in the induction and maintenance of the diseases (Fox et al., 2018; Ray et al., 2017). Since Ibudilast is already approved for asthma Phase II PoC studies with this drug in MDD could be easily initiated.

It is also worth mentioning in this context the recently observed target off effect of MIF in mediating unwanted metabolic effects of atypical antipsychotic therapy (Cui et al., 2018). As, in schizophrenic patients, the augment in BMI along with circulating concentrations of insulin, triglyceride and MIF provoked by olanzapine depended on a “normal” MIF producer genotype this paves the way for an additional indication of MIF inhibitors as co-treatment with atypical antipsychotic drugs in individuals with normal MIF expression.

Reverting to the preclinical setting, it seems of major relevance for the potential pathogenetic and therapeutic implications of this finding that DDT apparently mediates in a MIF-independent manner the antidepressant response to fluoxetine in mice (Samuels, 2014). The potential area of research of DDT in MDD is clearly very large and of potential significant impact for the better understanding of the role of the MIF family of cytokine in this disease. It will be important to understand whether in human MDD MIF and DDT may act independently as apparently occur in the mouse model or synergistically. This latter case should open novel therapeutic approaches for identification of a new class of dual inhibitors of MIF and DDT. The first of this dual inhibitor, 4-IPP (4-iodo-6-phenylpyrimidine), has proved effective in animal models of lung inflammation (Rajasekaran et al., 2014).

Simultaneous blockade of MIF and DDT could also be achieved with mAb directed their common receptor, CD74. One anti-CD74 mAb, named Milantuzumab, is in Phase II clinical setting for oncological indications (Berkova et al., 2010).

Selective inhibition of DDT has also shown to be feasible with a small molecule that has very recently been characterized and described. This compound and its eventual dervatives may be of particular interest for preclinical studies models of MDD (Tilstam et al., 2019)

In conclusion, our review aims at showing that besides its interaction with known pathways involved in the pathophysiology of depression, MIF also exerts pleiotropic immune and endocrine effects in the CNS and may have important roles in the pathogenesis of MDD independently on its effects on the depressive condition. Whilst studies in animal models are discordant, the studies in patients with MDD convergently indicate that MIF plays a role in induction and maintenance of the disease. Preclinical and clinical studies on the second member of the MIF family of cytokine, D-DT, are highly warranted both in preclinical models and human suffering from MDD.

5. Limitations

This is a narrative and not a systematic review of the literature on the involvement of MIF, in the etiopathogenesis and natural history of MDD and its possible role as therapeutic target. We have highlighted key studies performed in humans and in animal models, irrespective of population size and methodological approach. Additional studies are also needed on the second member of the MIF family named DDT that often displays synergistic function with MIF and their receptors.

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CRediT authorship contribution statement

Maria Cristina Petralia: Writing - original draft, Writing - review & editing. **Emanuela Mazzon:** Writing - original draft, Writing - review & editing. **Paolo Fagone:** Writing - review & editing. **Maria Sofia Basile:** Writing - review & editing. **Vittorio Lenzo:** Writing - review & editing. **Maria Catena Quattropani:** Writing - review & editing. **Klaus Bendtzen:** Writing - original draft, Writing - review & editing. **Ferdinando Nicoletti:** Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None to declare.

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