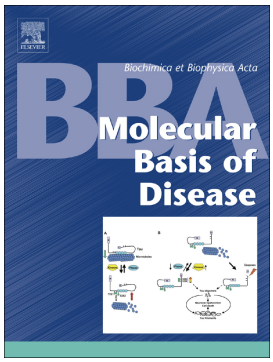

Mitochondria, endoplasmic reticulum and innate immune dysfunction in mood disorders: Do mitochondria-associated membranes (MAMs) play a role?

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Mitochondria, endoplasmic reticulum and innate immune dysfunction in mood disorders: do Mitochondria-Associated Membranes (MAMs) play a role?

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Abstract

Mood disorders like major depression and bipolar disorder (BD) are among the most prevalent forms of mental illness. Current knowledge of the neurobiology and pathophysiology of these disorders is still modest and clear biological markers are still missing. Thus, a better understanding of the underlying pathophysiological mechanisms to identify potential therapeutic targets is a prerequisite for the design of new drugs as well as to develop biomarkers that help in a more accurate and earlier diagnosis.

Multiple pieces of evidence including genetic and neuro-imaging studies suggest that mood disorders are associated with abnormalities in endoplasmic-reticulum (ER)-related stress responses, mitochondrial function and calcium signaling. Furthermore, deregulation of the innate immune response has been described in patients diagnosed with mood disorders, including depression and BD. These disease-related events are associated with functions localized to a subdomain of the ER, known as Mitochondria-Associated Membranes (MAMs), which are lipid rafts-like domains that connect mitochondria and ER, both physically and biochemically.

This review will outline the current understanding of the role of mitochondria and ER dysfunction under pathological brain conditions particularly in major depressive disorder (MDD) and BD that support the hypothesis that MAMs can act in these mood disorders as the link connecting ER-related stress response and mitochondrial impairment, as well as a mechanisms behind sterile inflammation arising from deregulation of innate immune responses. The role of MAMs in the pathophysiology of these pathologies and its potential relevance as a potential therapeutic target will be discussed.

1. Introduction

Brain diseases represent a considerable social and economic burden. In Europe, 1 out of 3 individuals will have at least one brain disorder, with estimated yearly costs of about 800 billion euros; amongst neuropsychiatric conditions, mood disorders, including unipolar depression and bipolar disorder (BD), represent the most costly entities, even exceeding dementia's burden [1].

The World Health Organization has declared that depression is now the world's leading cause of disability [2]. It is a common mental disorder, with about 1 in 5 people experiencing at least one depressive episode in their lifetime [3]. For many patients, the course illness is episodic, with inter-episodic remission. Nonetheless, a chronic course

is frequent, with 80% experiencing additional episodes, and the likelihood of recurrence increases with every episode [3]. Depressive symptoms can broadly group into emotional (e.g. depressed mood and anhedonia), neurovegetative (e. g. fatigue, insomnia and appetite changes), and cognitive symptoms, without characteristic manic symptoms that only occur in BD. While in mild cases of depression psychological treatment could be considered, depression of moderate and particularly severe intensity warrant pharmacological treatment [4]. Antidepressants classically enhance monoaminergic neurotransmission, with newer drugs targeting other brain systems [3], [5].

BD is a chronical mental disorder with a chronic relapsing and remitting course affecting around 2% of the population, characterized by mood swings between manic and depressive states with frequent cognitive and functional impairment, high health care costs and premature mortality [6]. Lifetime treatment is frequently necessary, and pharmacological therapy is often the first-line maintenance treatment to prevent recurrences of mood episodes in BD, using mood stabilizers (e.g. lithium and valproate) or atypical antipsychotics (e.g. quetiapine and aripiprazole), but also antidepressants for acute depressive phases [6]. Polypharmacy is common in BD due to the lack of single effective therapies, reflecting the gap between unmet clinical needs and current psychopharmacological research. Delayed diagnosis/misdiagnosis is frequent, especially in early phases of BD, given its onset is often characterized by a depressive episode, which can be clinically like unipolar depression [7]. Despite promising findings, no clinical or laboratorial biomarker has been clearly identified that allows for a diagnosis of BD or predicts the conversion from unipolar depression to BD [8].

Increased morbidity and mortality in mood disorders is multifactorial and complex: besides a well-known increase in suicide risk for both depression and BD, medical comorbidities such as cardiovascular disorders and metabolic conditions (e.g. diabetes, obesity) also take their toll [9-11]. The rate of metabolic syndrome (MS) is increased in mood disorders, even in its earliest phases, as found in the recent *Bipolar Illness Onset Study (BIO),* where MS risk was 3.5x higher in BD patients [12-14]. Metabolic-inflammatory changes have been proposed as a pivotal factor in the relation between BD and medical comorbidity [15]. The emerging association between depression and general medical comorbidities also seems to be bidirectional and potentially mediated by immune dysfunction [16]. Therefore, targeting the metabolic-inflammatory-mood pathway may potential yield improved outcomes in these mood disorders.

Impairment of endoplasmic-reticulum (ER)-related stress responses, mitochondrial dysfunction and innate immunity deregulation, which have been implicated in the pathophysiology of depression and BD, are associated with Mitochondria-Associated ER Membranes (MAMs). Since the role of these ER-mitochondria contacts in mood disorders is largely unknown it will be of utmost importance to unveil its impact on these psychiatric pathologies.

2. Mitochondrial dysfunction in mood disorders

The human brain has a high energy demand and the majority of energy used by the brain in the form of ATP is generated by mitochondria via mitochondrial oxidative phosphorylation. Brain mitochondria produce reactive oxygen species (ROS) that are relevant signaling molecules, buffer cytosolic Ca^{2+} in neurons, as well as regulate neurogenesis, neuronal plasticity and apoptosis [17]. These physiological events are strictly dependent on the close contact of mitochondria with ER [18]

Patients suffering from mitochondrial diseases caused by genetic alterations that affect metabolic activity frequently develop symptoms of major depressive disorder (MDD) and BD, psychosis, and personality changes [19-20] Furthermore, psychiatric symptoms such as depression are often prevalent years before the onset of cognitive and motor symptoms in patients later diagnosed with neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's disease [21], that present neuronal mitochondrial dysfunction as a major pathological hallmark [22].

Over the past ten years, several genome wide association studies (GWAS) have identified CACNA1C, a gene that codes for the α-subunit of the L-type Ca^{2+} channel as one of the strongest genetic risk factors for the development of mood disorders [23]. A recent work from Michels and colleagues (2018) demonstrated that siRNA-mediated knockdown of CACNA1C, preserved mitochondrial morphology, mitochondrial membrane potential, and ATP levels in neuronal cells after glutamate treatment [24]. These findings strongly support a link between mitochondrial alterations and mood diseases, which is reinforced by the role of Disrupted-in-schizophrenia 1 protein (DISC1), another putative risk factor for mood disorders, namely depression and BD [25], in mitochondrial homeostasis and transport [26]. DISC1 knockdown in SH-SY5Y cells decreased NADH dehydrogenase activity and ATP production and disassemble oxidative phosphorylation complexes [27]. Therefore, a major function of DISC1 in regulating mitochondrial distribution, ATP synthesis and calcium buffering may be disrupted in psychiatric diseases.

2.1. Mitochondrial dysfunction in bipolar disorder (BD)

According to the mitochondrial dysfunction hypothesis for BD [28], altered expression patterns of mitochondria-related genes in BD are caused by mutations/polymorphisms of mtDNA or chromosomal loci responsible for mitochondrial functions. The mtDNA polymorphism 10398A was associated with changes in mitochondrial Ca^{2+} signaling in BD patients [28-29]. Moreover, a genetic association between a complex I subunit gene and BD was reported [30].

Since the proposal of the mitochondrial hypothesis for BD in 2000 by Kato and Kato, many studies suggesting that mitochondrial dysfunction may play a key role in BD pathophysiology have been published [28]. Different post mortem studies reported decreased expression of genes encoding subunits of complex I, III, IV and V complexes of the electron transport chain (ETC) in the hippocampus [31] and in the prefrontal cortex from BD patients [32]. Consequently, impairment of complex I and increased protein oxidation and nitration were observed in the prefrontal cortex of these patients [33], as well as decreased levels of the mitochondrial uncoupling protein-2 (UCP2) mRNA [34]. A more recent study showed that neurons derived from induced pluripotent stem cells (iPSCs) of BD patients exhibited hyperexcitability associated with upregulation of mitochondrial genes, increased mitochondrial membrane potential, and decreased size of mitochondria [35]. Metabolic studies revealed increased levels of lactate and gamma-aminobutyric acid in gray matter of medication-free BD patients suggesting a shift in energy redox state from oxidative phosphorylation toward glycolysis in these patients [36].

In addition to energy production and Ca^{2+} homeostasis regulation, mitochondria are also crucial in regulating cell death and survival [22]. It has been recently reported a significant decreased in the levels of the anti-apoptotic proteins Bcl-xL, survivin and Bcl-xL/Bak dimer and a concomitant increase in active caspase-3 levels in peripheral blood mononuclear cells (PBMCs) isolated from BD patients [37]. Accordingly, BD brains were reported to present a significant increase in protein and mRNA levels of pro-apoptotic factors and a significant decrease in the levels of anti-apoptotic factors [38] that may contribute to brain atrophy and progressive cognitive changes in BD.

2.2. Mitochondrial dysfunction in major depressive disorder (MDD)

Genetic, proteomic and metabolic studies are emerging providing evidence that mitochondria-mediated mechanisms are associated with depression [39]. Gardner and colleagues (2003) reported that 68% of depressive patients have mtDNA deletions compared to 36% of control subjects [40]. Furthermore, a number of mitochondrial

genes have been recently implicated in depression, namely *TOMM40* and *MAO* genes that encode the central pore of the mitochondrial protein import apparatus and the mitochondrial isozymes monoamine oxidase A and B, respectively [41].

Disturbed oxidative phosphorylation and reduced mitochondrial ATP production may significantly contribute to impaired neuronal plasticity and neurogenesis, which are considered hallmarks in the neurobiology of depression [39]. It was demonstrated that in brain tissue from MDD patients ATP levels are decreased compared to healthy controls [42] and ATP turnover-related respiration was found decreased in PBMCs from depressed patients compared to aged-matched controls [43].

Mitochondria are the primary source of ROS through oxidative phosphorylation due to the leakage of electrons at the ETC. Excessive generation of ROS and/or depletion of antioxidant defenses lead to oxidative stress. Several studies support a close link between oxidative stress and depression. For example, increased oxidative damage and decreased mRNA and protein levels of the subunits of ETC complex I were detected in the cerebellum of MDD patients [44]. Also, decreased levels of non-enzymatic and enzymatic antioxidants have been reported in these patients [45].

Mitochondria are highly dynamic organelles that undergo permanent fission and fusion processes that are crucial for the transport, reorganization, and regeneration of these organelles within the cells. Impairments in the structural dynamics lead to reduced energy supply, accumulation of dysfunctional mitochondria and increased ROS production, which are closely associated with the risk of psychiatric disorders, including MDD [39]. Interestingly, increased expression of mitochondrial fission genes, FIS1 and DRP1 and decreased expression of the mitochondrial fusion genes, MFN1, MFN2 and OPA1 in frontal cortex and hippocampus have been associated to depressive behaviour in a rat model of diabetes [46].

3. ER stress and the Unfolded Protein Response (UPR) in mood disorders

The endoplasmic reticulum (ER) is a multifunctional organelle involved in multiple and crucial cellular processes, namely synthesis, folding, and maturation of secreted and transmembrane proteins, synthesis of phospholipids and steroids, and storage of Ca^{2+} ions in the ER lumen [47]. Several cellular insults such as oxidative stress, iron imbalance, leakage of Ca^{2+}, protein overload and hypoxia cause the accumulation of unfolded and/or misfolded proteins in the ER lumen triggering ER stress. In response, an extremely conserved signaling cascade termed the unfolded protein response (UPR), is activated and triggers a set of transcriptional and translational events (Figure 1) to promote cell adaptation to reestablish ER homeostasis and preserve cell survival

[48]. However, the cellular response outcomes are influenced by ER stress levels and duration [48]. Cells can cope with mild ER stress and reestablish normal ER functions. Conversely, when ER stress is excessive and prolonged, this adaptive response fails and a terminal UPR program commits cells to apoptosis [49]. Cell fate under mild and severe ER stress conditions rely on ER-mitochondria contacts and on the transfer of lipids and Ca^{2+} between both organelles [18].

The ER has been pointed out as the key player in several brain diseases, including neuropsychiatric disorders and a growing body of evidence has highlighted the crucial role of ER-related stress responses in the pathophysiology of mood disorders [50]. Indeed, it has been shown that pharmacological interventions for mood disorders are able to target UPR-related genes (e.g. [51]). For instance, valproate, carbamazepine and lithium are mood stabilizing drugs that upregulate ER chaperones and activate the unfolded protein response element (UPRE). Therefore, it can be hypothesized that the mode of action of these mood stabilizers involves UPR activation to reestablish homeostasis [52]. Interestingly, numerous authors have implicated genes that modulate the UPR pathway in the development of several mouse models of depression-like behaviour, such as those encoding calreticulin [53] and Bax inhibitor 1 [54].

3.1. Compromised ER stress response in BD

Genetic studies demonstrating a significant association between polymorphisms in ER stress-associated genes like *GRP78*, *XBP1* or *GRP94* (glucose-regulated protein, 94 kDa) and BD [55] further support the involvement of ER stress in the pathophysiology of this mood disorder. Accordingly, the polymorphism in the *XBP1* promoter was established as a genetic risk factor for the development of BD, since patient-derived cells containing this alteration have a compromised ability to cope with stress [56]. In addition, altered levels of several UPR-related signaling proteins have been described in samples obtained from BD patients. Under ER stress conditions, an increase in GRP78, P-eIF2α and CHOP levels was found in cultured lymphocytes from healthy controls but not in those obtained from BD patients and ER stress-induced cell death markers were significantly higher in patients than in controls, demonstrating that the response to stress is compromised in BD. Additionally, an altered ER stress response was shown in late-stage BD patients while the response in early-stage patients did not differ from healthy subjects [57].

3.2. Compromised ER stress response in MDD

Brown and colleagues reported the upregulation of ER stress-related proteins in individuals diagnosed with MDD who committed suicide when compared with MDD patients who died from other causes [58]. The association between stress-related mental disorders, in particular MDD, and systemic ER stress markers was corroborated by studies showing an increased expression of UPR-related genes, such as BIP, CHOP and XBP1s in leukocytes isolated from MDD patients [59]. Furthermore, elevated levels of EDEM1, which facilitates the degradation of misfolded proteins in response to ER stress, were found in leukocyte-derived RNA samples of MDD patients [59]. Interestingly, stress-related mental disorders, particularly MDD, have been linked to increased inflammation. Recently, it was demonstrated that the protein XBP1, in addition to its role in the ER stress response, is a key modulator of the innate immune response [60]. Therefore, it was hypothesized that higher levels of XBP1 may represent an adaptive response of MDD patients to elevated rates of inflammation [59]. ER stress may also provide a mechanistic link between mental disorders, namely MDD, and the associated physical comorbidities, in particular cardiovascular and metabolic diseases. Indeed, there are multiple lines of evidence suggesting that ER stress and subsequent UPR activation play a central role in the pathophysiology of cardiovascular disorders [61] and metabolic disorders such as diabetes and obesity [62]. Recently, the up-regulation of XBP1 has been associated with the development of cardiovascular and metabolic diseases since it modulates glucose and lipid metabolism [63].

4. Innate immunity in mood disorders

Innate immune cells and the inflammasome appear to be critical for the activation and orchestration of innate immunity. Recently, accumulating evidence has indicated that disturbances in the inflammatory response system not only provoke autoimmune disorders, but also can have deleterious effects on neuronal function and mental health. The cytosolic pattern recognition receptor (PRR) NOD-like receptor family, pyrin domain containing 3 (NLRP3) senses a wide range of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Upon activation, NLRP3 triggers the assembly of inflammasome via the self-oligomerization and the recruitment of apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) and pro-caspase-1, facilitating the robust immune responses including the secretion of proinflammatory cytokines (IL-1β and IL-18) and pyroptosis [64]. Many stimuli, including ER stress, mitochondrial dysfunction and production of

ROS, release of oxidized mtDNA or cardiolipin exposure, release of cathepsins after lysosomal destabilization, and alterations in Ca^{2+} homeostasis have been suggested as potential NLRP3 activating stimuli. Uncontrolled activation of NLRP3 inflammasome is one of the major causes of a variety of autoimmune, autoinflammatory and infectious diseases, as well as metabolic, cardiovascular and neurodegenerative diseases [65]. Recent findings also implicate the NLRP3 inflammasome in the neuroinflammatory states in psychiatric disorders, such as MDD and BD.

4.1. BD-associated changes in innate immunity

BD has been strongly associated with dysregulation of the immune system and inflammation [66] and patients with systemic autoimmune diseases have been shown to present a higher risk for BD [67]. Moreover, BD-related co-morbidities such as cardiovascular and metabolic diseases are associated to chronic inflammation [68].
Several studies have reported elevated peripheral levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), soluble interleukin-2 receptor (sIL-2R), interleukin (IL)-1β, IL-6, and soluble receptor of TNF-type 1 (STNFR1), among others (recently reviewed in [69]). In addition to peripheral alterations, it has been reported increased IL-1β and decreased IL-6 levels in the cerebrospinal fluid of BD patients compared to controls [70]. Accordingly, higher protein and mRNA levels of IL-1β, IL-1 receptor (IL-1R), nuclear factor-κB (NF-κB), and microglial activation markers have been reported in the postmortem frontal cortex of BD patients compared with control subjects [71].

Given that inflammasomes are the multiprotein complexes that directly mediate the innate immune system's responses to danger signals, their activation might be closely associated with the pathological mechanisms underlying BD [72]. BD patients seem particularly vulnerable to mitochondrial dysfunction and, subsequently, to an increase in mitochondrial ROS generation that can act as damage-associated molecular patterns (DAMPs) and positively regulate the levels of pro-inflammatory factors such as IL-1β, caspase-1 and NF-κB [73]. The NLRP3 inflammasome has been pointed out as a redox sensor of mitochondrial ROS production and as the structure behind immune innate activation. Kim and colleagues [74] found lower levels of complex I and NDUFS7, a subunit of complex I, concomitantly with higher levels of both mitochondrial NLRP3 and ASC, and increased levels of caspase-1, IL-1β, IL-6, TNFα and IL-10 in post-mortem frontal cortex samples from BD patients compared with healthy controls [74]. This study suggests that immune-activation in the BD brain is associated with mitochondrial dysfunction and NLRP3-inflammasome activation. More recently, Scaini

and colleagues [75] observed an upregulation of the gene expression levels of NLRP3, ASC, and pro-caspase 1 in peripheral cells isolated from BD patients, followed by an increase in caspase-1 activity as well as in IL-1β and IL-18 levels. Finally, Haneklaus and colleagues strengthened the enrollment of NLRP3 inflammasome in the BD pathophysiology by demonstrating that both NLRP3 inflammasome formation and IL-1β production are regulated by microRNAs that have been implicated in BD [76]. Given that inflammasome activation is regulated by specific membranous ER mitochondria microdomains [77], inter-organelle miscommunication can be anticipated as an upstream event of NLRP3 activation in BD.

4.2. MDD-associated changes in innate immunity

A strong link between inflammation and MDD is supported by numerous studies demonstrating increased inflammatory markers in MDD patients and a higher incidence of MDD in patients with inflammatory disease or in cytokine-treated patients.

Studies performed using human samples showed that patients with MDD exhibit several features of inflammation, including increased expression of pro-inflammatory cytokines and their receptors, acute phase proteins and chemokines, both in peripheral blood and cerebrospinal fluid (CSF) [78-80]. According to several meta-analyses, higher levels of pro-inflammatory cytokines such as TNF-α [79], IL-1β [80], IL-6 [80], IL-10, IL-13, IL-18, the soluble IL-2 receptor [79], [81] and C-reactive protein (CRP) are detected in individuals with MDD diagnosis [80].

Epidemiologically, immune-mediated diseases, such as inflammatory bowel disease [82], multiple sclerosis [82], rheumatoid arthritis [82], lupus erythematosus [83], diabetes [84], metabolic syndrome [85] and cardiovascular disease have been associated with higher MDD incidence [86].

Besides the studies demonstrating a correlation between inflammatory markers and MDD, it was also showed that similar symptoms can be developed by the administration of cytokines or cytokine inducers. Interferon-α therapies for several disorders such as hepatitis C, resulted in a higher incidence of MDD and a higher risk of having recurrent depressive episodes in patients who suffer from MDD [87]. Also, a unique systemic administration of LPS was found to increase depressive-like behaviour in humans [9]. Moreover, the administration of typhoid vaccine to healthy individuals produced MDD-similar brain alterations and symptoms [10].

The involvement of NLRP3 inflammasome activation has been also reported in MMD. Gene expression and protein levels of the NLRP3 inflammasome-associated proteins NLRP3 and caspase-1 are upregulated in peripheral blood mononuclear cells

of MMD patients [88-89]. Also, the levels of cytokines that are secreted upon activation of the inflammasome complex, IL-1β and IL-18, are elevated in the serum of these patients [89].

The involvement of NLRP3-inflammasome complex in the pathogenesis of MDD is further supported by findings demonstrating that in the absence of a NLRP3 inflammasome, prolonged stress does not provoke depressive behaviors or microglial activation in mice [90]. Accordingly, inflammasome inhibition after antidepressant treatment have been reported [91]. Furthermore, it was demonstrated that the pharmacological inhibition or genetic deficiency of caspase-1 in mice not only diminish depressive- and anxiety-like behaviours but also prevent the depressive-like behaviours triggered in response to chronic stress [92]. Altogether, these studies suggest that the inflammasome could be a target for new therapeutic interventions to prevent depression in patients.

5. Mitochondria-Associated Membranes (MAMs)

5.1. MAMs composition and function

Mitochondria-Associated Membranes (MAMs) are proteinaceous contact sites between the ER and mitochondria created by the physical interactions of proteins associated with both organelles. As the MAMs, unlike other organelles, were firstly isolated and described as a separate biochemical entity only in 1990 by Jean Vance, they can be considered as a new evolving hot topic in research.

These proteinaceous contact sites are created when the ER approaches at least the 20% of the mitochondrial surface with a distance of about 10-25 nm, depending respectively on whether the smooth ER or the rough ER is involved [11]. MAMs provide a fundamental platform for a wide variety of cellular functions and, for this reason, there are many proteins involved in these ER-mitochondria interactions: Ca^{2+} ion channels located in the ER or in the outer mitochondrial membrane (OMM) such as the inositol 1,4,5-trisphosphate receptor (IP3R), the ryanodine receptor (RyR) and the voltage-dependent anion channel 1 (VDAC1); the MAM-localized Sigma-1 receptor (Sigma-1R), an ER chaperone protein regulating cell survival and Ca^{2+} signaling between the two organelles; the Ca^{2+}-ATPase pump of the sarco/endoplasmic reticulum (SERCA); ER-resident chaperones such as calnexin (CNX), calreticulin and Grp78/BiP; enzymes involved in forming or cleaving disulphide bonds, such as protein disulphide isomerase (PDI), or involved in ER redox regulation such as ERO1α; enzymes involved in lipid biosynthesis and proteins for lipid transfer such as Fatty acid CoA ligase 4 (FACL4) and presenilins 1 and 2 (PS1/PS2); proteins of the UPR

signalling pathways such as PERK; proteins that regulate mitochondrial dynamics, responsible for mitochondrial size, length and shape like mitofusin 2 (MFN2) and the dynamin-related protein (DRP1); components of the inflammasome such as NLRP3 and its adaptor protein ASC [93-94] (Figure 2). Increasing evidence suggests that ER-mitochondria contact sites serve as an important cellular signalling platform associated with several important functions. MAMs are responsible for the transfer of lipids and Ca^{2+} between the ER and mitochondria and are thus involved in numerous cellular processes regulated including lipid biogenesis, proteostasis including the ER UPR and autophagy, Ca^{2+} signalling, inflammation, mitochondrial dynamics and bioenergetics, and apoptosis [93].

MAM is a lipid raft domain enriched in several phospholipid (PL)-synthesizing enzymes, such as phosphatidylserine (PS) and phosphatidylinositol (PI) synthases. In a normal model, the PS after being transferred to mitochondria is decarboxylated by PS decarboxylase in the inner mitochondrial membrane (IMM) to form phosphatidylethanolamine (PE). PE is then rapidly exported from the mitochondria to other organelles, such as the ER, where it is converted to phosphatidylcholine (PC). PS decarboxylase inhibition leads to a massive accumulation of PS in MAMs, thus confirming the involvement of the ER-mitochondria contacts in PS transfer. The ER-mitochondria interface is also the site of transfer of phosphatidic acid (PA) that is the precursor of cardiolipin (CL), a PL enriched in the IMM essential for mitochondrial bioenergetics and apoptosis induction, which is also a trigger of NLRP3 inflammasome activation upon translocation to the OMM. Although PA can be also synthesized by mitochondria, most of the PA used for CL synthesis originates from the ER and is thus transported through the MAM [95]. In addition to ER-to-mitochondria lipid transfer, MAMs are also involved in the transfer of Ca^{2+} from ER to mitochondria through the interaction of VDAC at the OMM with the IP_3R at the ER, which are linked by the molecular chaperone glucose-regulated protein (GRP75) [96]. Ca^{2+} is required for numerous mitochondrial functions, such as ATP synthesis and promotion of mitophagy and apoptosis. An efficient import of Ca^{2+} at MAMs is mediated by GRP75, which brings the openings of the IP_3R channels in ER near the VDAC in the OMM. The opening of the IP_3R is regulated by proteins present or recruited to MAMs, including calnexin, Sigma-1R, PS1 and PS2 [97].

5.1.1. MAMs and inflammation

Prolonged metabolic stress in cellular organelles, namely ER and mitochondria, can trigger an inflammatory response. Transcription of genes encoding pro-

inflammatory cytokines was shown to be activated by mediators of the three UPR branches upon chronic ER stress [98-99]: IRE-1α was found to trigger XBP1-mediated upregulation of TNF-α and interferon beta (IFN-β) and to increase IL-1β production; PERK was demonstrated to promote IL-6 production and ATF-6 was shown to induce the expression of IL-1β, IL-6 and TNF-α and to inhibit NF-kB-mediated anti-inflammatory signalling pathways [77]. This inflammatory response induced under irremediable ER stress conditions has been shown to involve activation of the NLRP3 inflammasome [100]. Mitochondria components released or exposed in response to dysfunction or damage can be directly recognized by receptors of the innate immune system and trigger an immune response. In fact, mitochondrial stress was shown to act upstream of NLRP3 inflammasome activation by providing DAMPs to trigger NLRP3 oligomerization, such as ROS, oxidized mtDNA or cardiolipin, or by inducing α-tubulin acetylation to relocate mitochondria to the proximity of NLRP3, increasing the production and secretion of pro-inflammatory cytokines [77].

The NLRP3 inflammasome is a protein complex composed of the receptor NLRP3 on the ER side and the adaptor apoptosis-associated speck-like protein containing a CARD on the mitochondrial side that induces caspase-1-dependent maturation of proinflammatory cytokines such as IL-1β and IL-18. Recent evidences demonstrated that NLRP3 relocates from ER to MAMs and is activated by MAM-derived effectors to promote an inflammatory response [101]. NLRP3 may be strategically placed on or in close proximity to these subcellular compartments to both sense danger signals originating from these organelles and use the compartment as a scaffold to assemble the complex.

Because MAMs provide a platform for NLRP3 inflammasome activation and subsequent secretion of pro-inflammatory mediators [77] and given their importance in cell life/death decisions, increasing evidence suggests that alterations of the ER-mitochondria axis could be responsible for the onset and progression of several diseases, including cancer, diabetes, obesity and neurodegenerative disorders [47].

5.2. Evidence for MAM alterations in mood disorders

Since MDD and BD are associated with compromised mitochondrial function and impairment of ER stress and innate immune responses, as described above, it can be hypothesized that dysfunction of the signalling platforms MAMs can be implicated in the pathophysiology of these mood disorders (Figure 3). Several recent evidences support this hypothesis that deserves to be deeply explored.

Sigma-1R, an intracellular chaperone that is highly enriched at the ER-mitochondria interface modulates inter-organelle Ca^{2+} signalling and bioenergetics [102]. Another role of Sigma-1R is to facilitate stress signalling from the ER to the nucleus thereby increasing intracellular levels of anti-stress and antioxidant proteins. Upon cellular stress, Sigma-1R interacts with numerous receptors, ion channels, kinases and various master regulator proteins residing in ER, MAM, nucleus or in the cytosol to mobilize and fine-tune anti-stress responses [103]. In the last two decades a considerable amount of clinical data demonstrated the role of Sigma-1R in various pathologies such as many neuropsychiatric disorders [104]. Ample evidence, including the presence of genetic variants within *SIGMAR1* and the interaction of numerous antidepressants with these receptors, suggested a role of Sigma-1R in mood disorders [105-106]. Accordingly, a preliminary study conducted by Shimizu and colleagues (2013) demonstrated that the Sigma-1R levels in plasma increases following antidepressant treatment in patients with MDD [107]. Furthermore, Sigma-1R knockout mice demonstrate a depressive-like phenotype [108]. Currently, some drugs (e.g., fluvoxamine, fluoxetine, escitalopram, donepezil, ifenprodil), which have been used in humans, and some endogenous neurosteroids (e.g. dehydroepiandosterone) have high to moderate affinity to Sigma-1R and exert antidepressant-like and neuroprotective actions supporting their clinical implication in numerous neuropsychiatric diseases [106].

Disrupted-in-schizophrenia 1 (DISC1) is a scaffold protein that is involved in the function of intracellular organelles and is linked to cognitive and emotional deficits. DISC1 variants (haplotypes, single nucleotide polymorphisms and copy number variations) have been associated with BD and MMD [25]. Interestingly, DISC1 is enriched in MAMs and interacts with IP3R1 modulating ER-mitochondria Ca^{2+} transfer. In mouse cortical neurons, DISC1 dysfunction has been shown to disrupt Ca^{2+} transfer and lead to abnormal Ca^{2+} accumulation in mitochondria following oxidative stress, affecting mitochondrial functions [109]. Moreover, it was demonstrated that DISC1 acts as an important regulator of mitochondrial dynamics in both axons and dendrites to mediate the transport, fusion, and cross-talk between ER and mitochondria, and pathological DISC1 isoforms, which are important genetic risk factors for mood disorders, disrupt this critical function [110]. These findings further support the impairment of MAMs in these psychiatric disorders.

Translocator protein (TSPO) is an 18 kDa membrane protein expressed in the outer mitochondria membrane in the central and peripheral nervous systems that is involved in the translocation of cholesterol into the mitochondria, which was recently

described as a MAM-resident protein. In the brain, TSPO has been extensively used as a biomarker of injury and inflammation. Indeed, TSPO is up-regulated in several inflammatory and neurodegenerative diseases and recent evidences also implicate this protein in neuropsychiatric disorders such as MDD and BD [111]. New findings demonstrate that TSPO-VDAC complex is upregulated in PBMCs from BD patients simultaneously with downregulation of mitophagic proteins and NLRP3 inflammasome activation suggesting that these MAM-located complex could lead to an accumulation of dysfunctional mitochondria, resulting in inflammation in this mood disorder [75].

6. Conclusions

Cellular modelling in BD and MDD has been proven useful to understand their biological basis, and abnormalities in mitochondrial function, ER-related stress responses, Ca^{2+} signalling, glia and immune cell signalling, as well as oxidative stress, inflammasome activation, autophagy and apoptosis have consistently been reported. Interestingly, these events are associated with functions localized to a subdomain of the ER, known as MAMs, which is a lipid raft-like domain close to mitochondria in such a way that the two organelles can physically and biochemically communicate with each other. ER-mitochondria juxtaposition is crucial for efficient inter-organelle Ca^{2+} transmission controlling mitochondrial bioenergetics and pro-survival/pro-death pathways and determining cell fate under stressful conditions. MAMs have been recently shown to regulate mitochondrial shape and motility, energy metabolism and redox status and to be central to modulation of various key processes like ER stress, autophagy and inflammasome signalling. Given MAM's importance in cell life/death decisions and immune responses, increasing evidence suggests that alterations of the ER-mitochondria axis could be responsible for the onset and progression of several diseases, including cancer, diabetes, obesity and neurodegenerative disorders. In this paper, we reviewed the evidences supporting that ER-mitochondria contacts at MAMs can be affected in the context of psychiatric diseases, namely BD and MDD. Elucidating the role of MAMs in the pathophysiology of these pathologies could have profound implications for drug development and treatment.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Figure 1 - ER stress-induced unfolded protein response (UPR). The UPR activation involves signalling pathways mediated by three ER stress sensors: PERK, IRE1α and ATF6. Under basal conditions, these sensors interact with the ER resident chaperone BiP (also known as GRP78), preventing transduction of UPR signals. In case of misfolded/unfolded proteins accumulation in the ER lumen, BiP dissociates from these sensors to bind abnormal proteins and UPR pathways are activated.
PERK: The dissociation of BiP from the ER luminal domain of PERK triggers its activation by dimerization and autophosphorylation. Once activated, PERK phosphorylates eIF2α, which in turn inhibits the translation of mRNAs, reducing the load of newly synthesized proteins in the ER. However, some mRNAs are preferentially translated because of their resistance towards the action of PERK/p-eIF2α. One of such mRNAs encodes ATF4, which promotes cell survival by inducing the expression of several genes involved in restoration of ER homeostasis. Under severe/prolonged ER stress conditions, ATF4 induces the expression of the pro-apoptotic protein CHOP. ***Ire1α***: The release of BiP from the ER luminal domain of IRE1α triggers its dimerization and autophosphorylation. Upon activation, IRE1α catalyzes a non-conventional splicing of the mRNA that encodes XBP1 leading to the expression of its active and stable form known as XBP1s. This spliced form of XBP1 upregulates chaperones and specific enzymes involved in phospholipid synthesis and promotes ER quality control processes by increasing the expression of ERAD components. ***ATF6:*** The dissociation of BiP from the ER luminal domain of ATF6 triggers its transport into the Golgi apparatus, where the cytoplasmic N-terminal domain of ATF6 is phosphorylated and cleaved. The released cytoplasmic domain is translocated to the nucleus, where it regulates the expression of ER chaperones, such as BiP, ERAD- and autophagy-related genes, and of proteins involved in organelle biogenesis.

Abbreviations: ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; BiP, binding immunoglobulin protein; CHOP, pro-apoptotic transcription factor C/EBP homologous protein; eIF2α, eukaryotic translation-initiation factor 2α; ERAD, ER-associated degradation; IRE1α, inositol-requiring enzyme 1 alpha ; PERK, PKR-like endoplasmic reticulum kinase; XBP1, X-box binding protein 1; XBP1s, spliced XBP1.

Figure 2 - Structure and function of components of Mitochondria-Associated Membranes (MAMs). Representation of proteins located at ER-mitochondria contacts that regulate organelle dynamics (MFN1/2), Ca^{2+} signalling (PML, AKT, PP2A, CNX, SERCA, GRP75, IP3R, VDAC1, MCU and Sig1R), ER redox regulation (PDI and ERO1α), exchange of phospholipid namely PC, PE and PS (FACL4, PEMT, PSD), unfolded protein response (UPR) signalling (PERK, BiP) and imune response (NLRP3 and its adaptor protein ASC; MAVS, STING and RIG1) at MAM interface. Abbreviations: ACS, caspase-recruitment domain; AKT, protein kinase; BiP, binding immunoglobulin protein; CNX, calnexin; ER, endoplasmatic reticulum; ERO1α, endoplasmic reticulum oxidoreductase-1 alpha; FACL-4, fatty acid CoA ligase 4; GRP75, glucose regulated protein 75; IMM, inner mitochondrial membrane; IP3R, inositol 1,4,5 trisphosphate receptor; MAM, mitochondria-associated membrane, MAVS, mitochondrial antiviral-signalling protein; MCU, mitochondrial calcium uniporter protein; MFN1/2, mitofusin 1/2; NLRP3, NOD-like receptor protein 3; OMM, outer mitochondrial membrane; PC, phosphatidylcholine; PDI, protein disulphide isomerase; PE, phosphatidylethalonamine; PEMT, PE N-methyltransferase; PERK, PKR-like endoplasmic reticulum kinase; PML, promyelocytic leukemia protein; PP2A, protein phosphatse 2A; PS, phosphatidylserine; PSD, PS descarboxylase; RIG1, retinoic acid-inducible gene-1; SERCA, sarco/endoplasmatic reticulum Ca^{2+}

ATPase; Sig1R, sigma-1 receptor; STING, stimulator of interferon genes; VDAC, voltage-dependent anion channel.

Figure 3- The "Mitochondria-associated Membrane (MAM) Hypothesis" for BD and MMD. DISC1, a putative risk factor for BD and MMD is enriched in MAMs and interacts with the IP3R1 modulating ER-mitochondria Ca^{2+} transfer. Sigma-1R is another MAM-resident Ca^{2+} modulator that has been associated with BD and MMD pathophysiology. Thus, it can be hypothesized that changes in Sigma-1R and DISC1 can be involved in the disruption of ER-mitochondria contacts at MAMs leading to the deregulation of Ca^{2+} homeostasis as well as to the impairment of stress and inflammatory responses. Perturbation of the ER response to stress triggered by disease-associated DISC1 and/or Sigma-1 alterations can affect the levels of UPR signalling mediators (e.g. p-eIF2α and XBP1s) and chaperones (BiP) leading to persistent ER stress with upregulation of pro-apoptotic transcription factors (e.g. CHOP). In addition, enhanced ER-to-mitochondria Ca^{2+} transfer can lead to mitochondrial Ca^{2+} overload, loss of mitochondrial membrane potential, ATP depletion and increased ROS accumulation, which in turn can lead to NLRP3 inflammasome activation and subsequent release of pro-inflammatory cytokines such as IL-1β. Furthermore, upregulation of TSPO in these pathological conditions can affect the formation of a TSPO-VDAC complex at MAMs that will promote mitochondria dysfunction and contribute to activation of an inflammatory response.
Abbreviations: ACS, caspase-recruitment domain; ATF6, activating transcription factor 6; BiP, binding immunoglobulin protein; Disrupted-in-schizophrenia 1 protein, DISC1; eIF2α, eukaryotic translation-initiation factor 2α; ER, endoplasmic reticulum; IL, interleukin; IP3R, inositol 1,4,5 trisphosphate receptor; IRE1α, inositol-requiring enzyme 1 alpha; MAM, mitochondria-associated membrane, NLRP3, NOD-like receptor

protein; PERK, PKR-like endoplasmic reticulum kinase; ROS, reactive oxygen species; Sig1R, sigma-1 receptor; TSPO, Translocator protein; VDAC, voltage-dependent anion channel; XBP1, X-box binding protein 1; XBP1s, spliced XBP1.

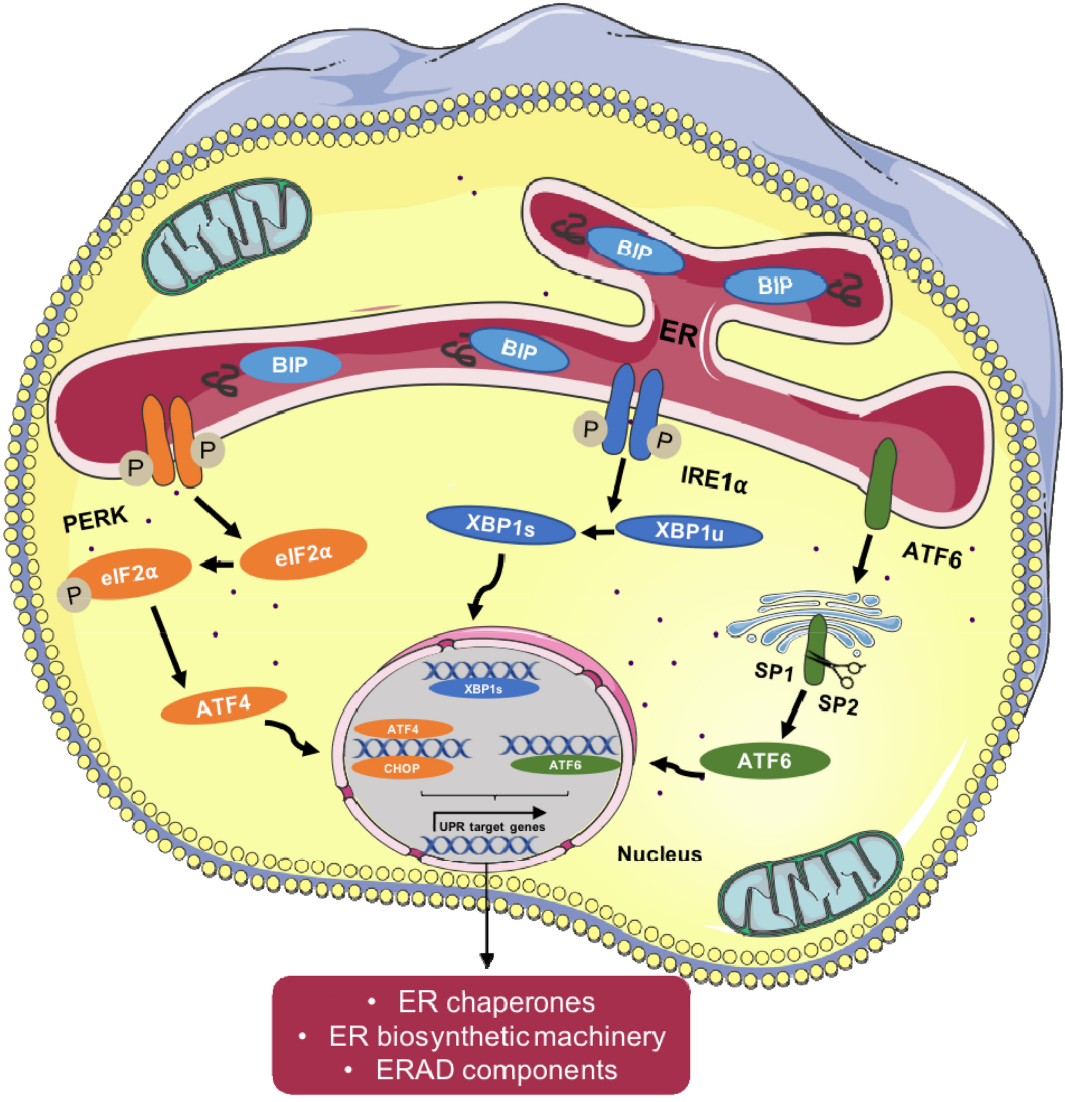
Highlights

Mood-disorders are associated with ER stress and mitochondrial dysfunction.

Inflammation has been implicated in mood-disorders.

MAM-resident proteins have been associated to bipolar and major depressive disorders.

MAMs can be involved in the pathophysiology of bipolar and major depressive disorders.


BIP
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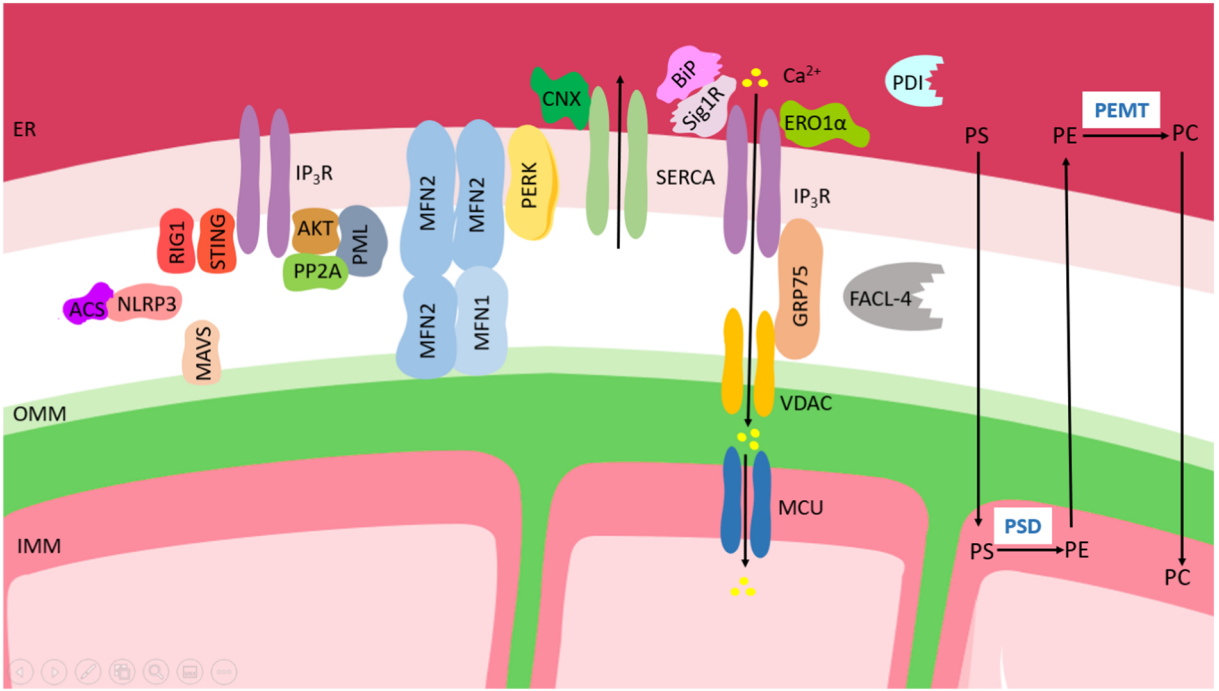
PERK
IRE1α
XBP1s
XBP1u
ATF6
eIF2α
P
eIF2α
ATF4
SP1
SP2
XBP1s
ATF4
CHOP
ATF6
ATF6
UPR target genes
Nucleus
• ER chaperones
• ER biosynthetic machinery
• ERAD components

Figure 1


ER
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IMM
IP3R
RIG1
STING
AKT
PML
PP2A
ACS
NLRP3
MAVS
MFN2
MFN2
MFN2
MFN1
PERK
CNX
SERCA
BiP
Sig1R
Ca2+
ERO1α
PDI
IP3R
GRP75
FACL-4
VDAC
MCU
PS
PE
PC
PEMT
PSD
PS
PE
PC

Figure 2

Mitochondrial dysfunction

Ca^{2+} overloading
Membrane depolarization
ATP depletion
ROS production

Inflammasome activation

IL-1β release
IL-18 release

Impaired ER stress response

Increased expression of:
Chaperones
Transcription factors
Apoptotic proteins

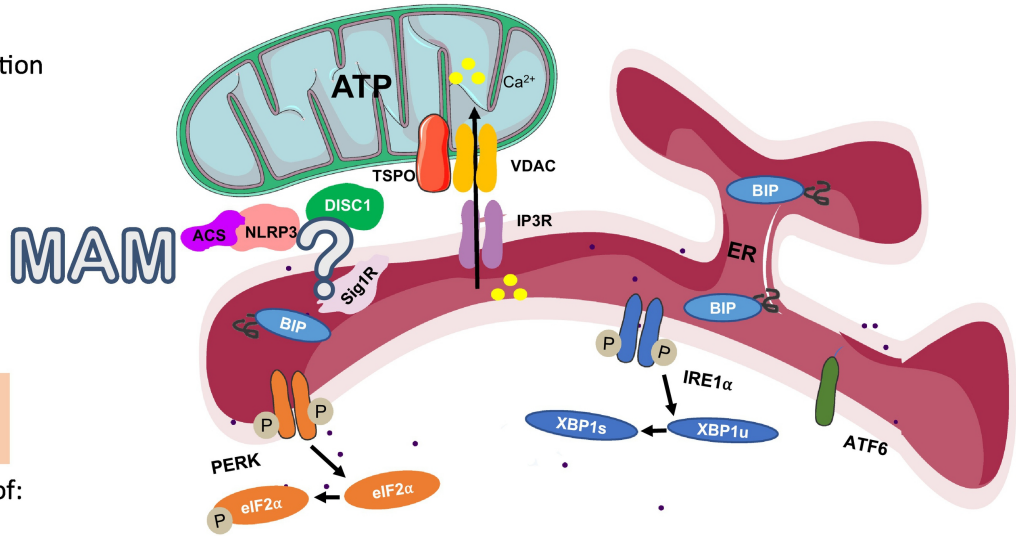

Figure 3