

# Endo-Lysosomal and Autophagy Pathway and Ubiquitin-Proteasome System in Mood Disorders: A Review Article

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**Abstract:** Mood disorders are disabling conditions that cause significant functional impairment. Due to the clinical heterogeneity and complex nature of these disorders, diagnostic and treatment strategies face challenges. The etiology of mood disorders is multifactorial, involving genetic and environmental aspects that are associated with specific biological pathways including inflammation, oxidative stress, and neuroprotection. Alterations in these pathways may reduce the cell's ability to recover from stress conditions occurring during mood episodes. The endo-lysosomal and autophagy pathway (ELAP) and the ubiquitin-proteasome system (UPS) play critical roles in protein homeostasis, impacting neuroplasticity and neurodevelopment. Thus, emerging evidence has suggested a role for these pathways in mental disorders. In the case of neurodegenerative diseases (NDDs), a deeper understanding in the role of ELAP and UPS has been critical to discover new treatment targets. Since it is suggested that NDDs and mood disorders share clinical symptomatology and risk factors, it has been hypothesized that there might be common underlying molecular pathways. Here, we review the importance of the ELAP and UPS for the central nervous system and for mood disorders. Finally, we discuss potential translational strategies for the diagnosis and treatment of major depressive disorder and bipolar disorder associated with these pathways.

**Keywords:** mood disorders, endo-lysosomal pathway, ubiquitin-proteasome system, autophagy, endo-lysosome, neuroplasticity, novel treatments, treatment target, translational science

## Introduction

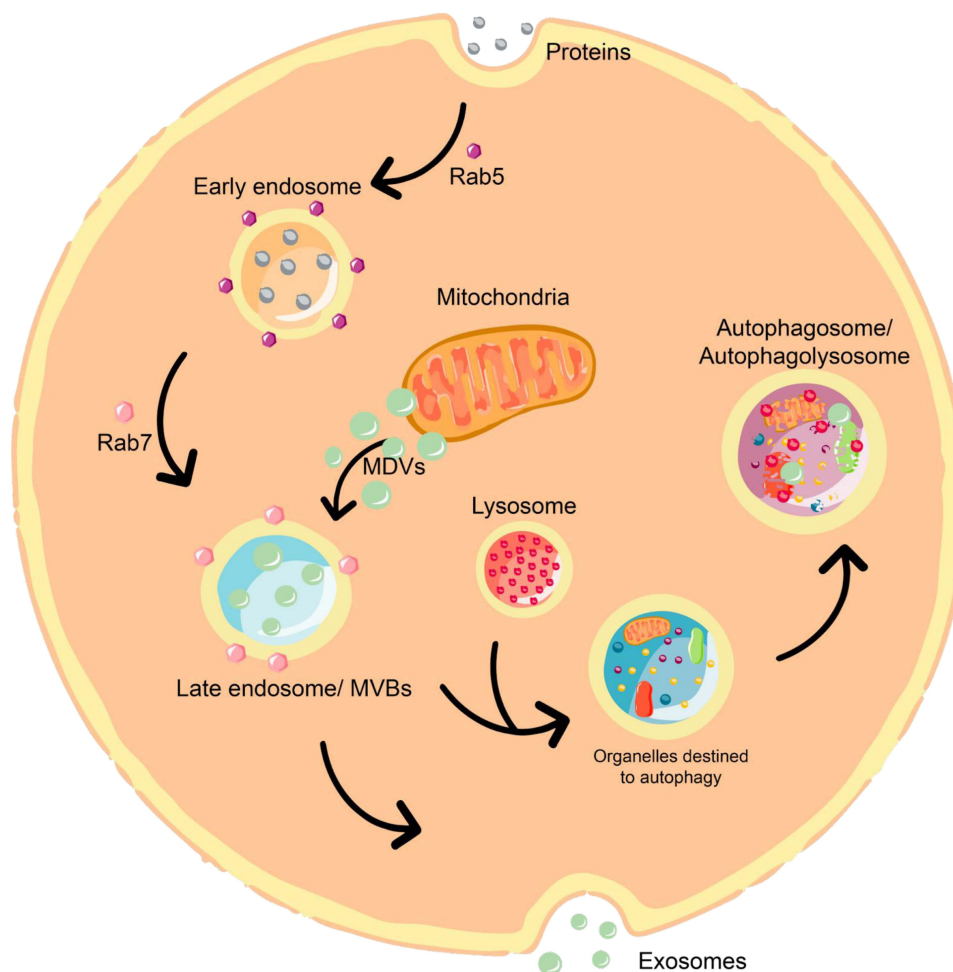
The term mood disorders is used to describe psychiatric conditions presenting with changes in emotional states. Bipolar disorder (BD) and major depression disorder (MDD) are among the most studied mood disorders that cause significant functional impairment.<sup>1,2</sup> Although the etiology of mood disorders has not been completely elucidated, it has been proposed that both environmental and genetic factors may underlie their pathophysiology.<sup>1,2</sup> Regarding the contribution of genetic factors, the role of multiple genes showing small size effects is the most acceptable model. For the environmental conditions, several risk factors have been associated with increased risk of developing MDD and BD including, early adverse stress, psychological stressors, and drug abuse.<sup>3–5</sup> The combination of environmental and genetic factors may lead to intermediate phenotypes, such as altered brain gene expression and circuitry dysfunction, that affect mood disturbances.<sup>6</sup> These alterations may be associated with changes in different cellular pathways that culminate in inflammation,<sup>7,8</sup> decreased neuroplasticity,<sup>9</sup> increased oxidative stress,<sup>10</sup> and cell death.<sup>11</sup> The endo-lysosomal and autophagy pathway (ELAP) and the ubiquitin-proteasome system (UPS) play critical roles in maintaining cellular homeostasis by controlling the quality and trafficking of the proteins. Since protein quality is crucial for the pathways involved in mood disorders, recent discoveries have shed light on the role of ELAP and UPS in these disorders.

The presence of misfolded proteins in specific brain regions are pathological hallmarks of neurodegenerative diseases (NDDs) including Alzheimer's disease (AD).<sup>12</sup> For this reason, the role of ELAP and UPS in NDDs is well recognized<sup>13,14</sup>

and has offered a starting point for new possibilities for the treatment of these diseases.<sup>15</sup> Clinically, NDDs patients show psychiatric and behavioral alterations in addition to cognitive impairment.<sup>16</sup> Furthermore, a recent follow-up study showed that having a mental disorder (especially MDD and BD) can increase the risk of developing dementia later in life.<sup>17</sup> Shared clinical symptoms and the fact that mood disorders may increase the risk for NDDs suggest that common molecular mechanisms may underlie mental disorders.<sup>16</sup> Although the contribution of specific molecular pathways has been addressed, a subset of MDD patients does not respond to current pharmacological treatments available.<sup>1</sup> Furthermore, the diagnosis and management of MDD and BD suggest that patients may benefit from new treatment strategies. A better understanding of the molecular pathways involved in mood disorders can bring insights into novel translational strategies for their diagnostic and treatment. Here, we review the importance of ELAP and UPS to the brain and the findings on their role in MDD and BD. Ultimately, we discuss potential translational strategies for mood disorders involving these cellular pathways.

## Endo-Lysosomal and Autophagy Pathway in Mood Disorders

The ELAP is a network for protein trafficking and degradation (Figure 1). Its goal is homeostasis maintenance, and this is especially important in neurons.<sup>13,18</sup> This system is composed of mitochondria, lysosomes, endosomes, and exosomes. Several studies have found that failure in one of these components is associated with mental illness due to aberrant protein sorting. In the following topics, we detail the findings related to the ELAP in mood disorders for each of its components.



**Figure 1** The endo-lysosomal and autophagy pathway. The process of endocytosis is regulated by a Rab GTPase called rab5, which helps with protein internalization and endosome maturation, trafficking, and signaling. Once the early endosome is formed, the process of maturation continues, the rab5-to-rab7 conversion underlies the cargo transition from early to late endosomes/ MVBs. This process is also mediated by mitochondria, which send MDVs for the formation of MVBs. The endocytic pathway has two main routes: either the MVBs can fuse with autophagosomes, together with lysosomes leading to the autophagic process; or merge to the plasma membrane and release their vesicles into the extracellular space, which will later be called exosomes.

**Abbreviations:** MVBs, Multivesicular bodies; MDVs, Mitochondria-derived vesicles.

## Mitochondria and Mitophagy

It is well known that mitochondria are responsible for maintaining cells' integrity and functioning through ATP production.<sup>19</sup> Additionally, mitochondria play a role in the quality control of cellular molecules. Under stress conditions, the first response of this organelle is the formation of vesicles containing mitochondrial DNA and proteins that are targeted to the endo-lysosomal system.<sup>20</sup> This reaction is an alternative stress response, functioning as a quality control mechanism. Furthermore, stress conditions can lead to mitochondrial dysfunction, which has been related to lysosomal impairment,<sup>21</sup> inflammatory responses,<sup>22</sup> and accumulation of autophagy substrates.<sup>23</sup> The following response under persistent stress conditions is the clearance of the damaged mitochondria (mitophagy).<sup>24,25</sup> Mitophagy failure is detrimental to neurons and brain function.<sup>26</sup> Its dysfunction can disturb mitochondrial functioning leading to the accumulation of defective organelles.<sup>27</sup>

Because of the sensitivity of the mitochondria to stress conditions, mitochondrial impairment has been largely studied in mood disorders.<sup>28,29</sup> Recent studies have hypothesized the involvement of the mitochondria in the progression and severity of MDD and BD.<sup>30</sup> A study focusing on the dorsolateral prefrontal cortex (dlPFC) from MDD patients found differentially expressed mitochondrial genes (Table 1) and several of these genes participate in regulatory processes of the nervous system.<sup>31</sup> In BD, mitochondrial alterations were associated with calcium signaling, a decrease in energy production, production of reactive oxygen species (ROS), and impairment of mitochondrial dynamics.<sup>32–34</sup> Mitochondria-related changes have also been found in the peripheral tissue of BD and MDD patients. Copy number variations in mitochondrial DNA are observed in patients with BD<sup>35,36</sup> and MDD.<sup>37</sup> Additionally, a study found changes in the levels of mitochondria proteins associated with the severity of MDD including MFN2, FIS-1, LC3B, Pink, and parkin.<sup>38</sup> A question remains whether these findings could be used to predict new episodes or function as biomarkers to measure disease severity.

Another way to address mitochondrial changes in the nervous system is using induced pluripotent cells (iPSCs) differentiated into neural cells. This approach gives us the opportunity of understanding the mechanisms that may be occurring in the brain of psychiatric patients. In BD, studies using iPSCs suggests alterations in mitochondria-related calcium signaling and alterations in mitochondrial size, function, and overexpression of mitochondrial-genes.<sup>39,40</sup>

Regarding mitophagy, one study showed that damaged mitochondria located in axons can trigger this pathway within tens of minutes.<sup>41</sup> This suggests that mitophagy dysregulation is associated with synaptic failure and consequently the development/progression of mental disorders.<sup>24,42</sup> In BD patients, findings show an upregulation of gene expression and protein levels of TSPO and VDAC (Table 1).<sup>43</sup> Interestingly, higher levels of TSPO reduce mitophagy.<sup>43</sup> These proteins, in addition to Pink1 and Beclin1, were decreased in a MDD rat model.<sup>44</sup> Interestingly, while levels of Pink1 were elevated, parkin levels were lower in the peripheral blood of MDD subjects.<sup>38</sup> It is possible that mitophagy is dysregulated in mood disorders, which may lead to mitochondrial accumulation and damage.

## Autophagy

Whereas mitophagy is a clearance pathway for mitochondria, the degradation of the whole cell is called autophagy. Autophagy is a lysosome-dependent cell death system that degrades and recycles damaged organelles and unfolded proteins.<sup>45</sup> Interestingly, treatment with silibinin inhibits autophagy and protects AD animal models from exhibiting anxiety/depression-like behaviors.<sup>46</sup>

Recent findings have suggested a role of autophagy in MDD pathophysiology and treatment.<sup>47,48</sup> Analysis of gene expression data from different databases showed an association of autophagy-related genes with MDD (Table 1).<sup>49</sup> Furthermore, these genes were associated with the immune microenvironment in MDD, which is a well-known pathway related to this disorder.<sup>50</sup> Additionally, glucocorticoids can negatively regulate autophagy pathway.<sup>48</sup>

In BD, alterations of the signaling pathway mammalian target of rapamycin (mTOR) have been addressed.<sup>51,52</sup> A transcriptome study of the prefrontal cortex (PFC) showed that genes related to the mechanistic target of the mTOR pathway were downregulated in patients while genes interrelated with the mTOR were upregulated (Table 1).<sup>53</sup> Additionally, gene co-expression network analyses showed an enrichment of mTOR signaling and mTOR-related signaling pathways in endothelial and neuronal cells.<sup>53</sup> This suggests the participation of different cell types in mTOR pathways in the PFC of BD subjects. Additional findings show the decreased activity of mTOR through the reduction of ULK1 kinase protein phosphorylation, which caused increased autophagy in cortical neurons of the PFC in BD patients.<sup>54</sup>



Table 1 (Continued).

	ELAP				UPS	
	-	-	hsa-miR-330-5p ↑	Exosome trafficking	<i>PSMD2</i>	Proteasome
	-	-	hsa-miR-1304-5p ↑		<i>PSMD6</i>	
	-	-	hsa-miR-511-5p ↑		<i>PSMA1</i>	
	-	-	hsa-miR-22-5p ↑		<i>PSMB8</i>	
	-	-	hsa-miR-331-3p ↑		<i>PSMB9</i>	
	-	-	hsa-miR-96-5p ↑		<i>PSMD13</i> ↓	
	-	-	hsa-miR-19a-3p ↑		-	
	-	-	hsa-let-7a-3p ↑		-	
	-	-	hsa-miR-32-5p ↑		-	
	-	-	hsa-miR-30c-5p ↑		-	
	-	-	hsa-miR-421 ↑		-	
	-	-	hsa-miR-361-5p ↑		-	
	-	-	hsa-miR-625-3p ↑		-	
	-	-	hsa-let-7b-3p ↑		-	
	-	-	hsa-miR-495-3p ↑		-	
	-	-	hsa-miR-494-3p ↑		-	
	-	-	hsa-miR-641 ↑		-	
	-	-	hsa-miR-340-3p ↑		-	
	-	-	hsa-miR-335-3p ↑		-	
	-	-	hsa-miR-139-5p ↑		-	
	-	-	hsa-miR-126-3p ↑		-	
	-	-	hsa-miR-204-5p ↑		-	
	-	-	hsa-miR-517a-3p ↑		-	
	-	-	hsa-miR-519a-5p ↑		-	
	-	-	hsa-miR-100-5p ↓		-	
	-	-	hsa-miR-4497 ↓		-	
	-	-	hsa-miR-769-5p ↓		-	
	-	-	hsa-miR-127-5p ↓		-	
	-	-	hsa-miR-1268a ↓		-	
	-	-	hsa-miR-378c ↓		-	
	-	-	hsa-miR-378d ↓	-		
	-	-	hsa-miR-7704 ↓	-		
	-	-	hsa-miR-3656 ↓	-		
	-	-	hsa-miR-4488 ↓	-		
	-	-	hsa-miR-17-3p ↓	-		
	-	-	hsa-miR-184 ↓	-		
	-	-	hsa-miR-144-3p ↓	-		
	-	-	hsa-miR-206	-		
BD	<i>Parkin</i> ↓	<i>Parkin</i> ↓	-	Mitophagy	<i>UBE2G1</i> ↓	E2
	<i>p62/SQSTM1</i> ↓	<i>p62/SQSTM1</i> ↓	-		<i>HIP2</i> ↓	
<i>LC3A</i> ↓	<i>LC3A</i> ↓	-	<i>FLJ11011</i> ↓			
<i>TSPO</i> ↑	<i>TSPO</i> ↑	-	-			
<i>VDAC</i> ↑	<i>VDAC</i> ↑	-	-			
-	<i>ASC</i> ↑	-	-			
-	<i>pro-casp1</i> ↑	-	-			
-	<i>caspase1</i> ↑	-	-			
-	<i>NLRP3</i> ↑	-	Inflammation			

(Continued)

Table I (Continued).

	ELAP				UPS	
-	-	-	hsa-miR-4516 ↑	Exosome trafficking	<i>CUL1</i> ↓	E3
-	-	hsa-miR-29c-3p ↑	<i>PIAS1</i> ↑↓		E3	
-	-	hsa-miR-22-3p ↑	<i>PIAS2</i> ↑			
-	-	hsa-miR-7977 ↑	<i>PIAS3</i> ↑			
-	-	hsa-miR-142-3p ↑	<i>PIAS4</i> ↑			
-	-	hsa-miR-1185-2-3p ↑	<i>WWP1</i> ↓			
-	-	hsa-miR-6791-5p ↑	<i>TRIM23</i> ↓			
-	-	hsa-miR-3194-5p ↑	<i>PJA2</i> ↓			
-	-	hsa-miR-6090 ↑	<i>PCGF4</i> ↓			
-	-	hsa-miR-21-5p ↑	<i>HIP2</i> ↓			
-	-	hsa-miR-3135b ↑	<i>VPS41</i> ↓			
-	-	hsa-miR-92a-3p ↑	<i>UBE3A</i> ↓			
-	-	hsa-miR-92a-3p ↑				
-	-	hsa-miR-7975 ↑				
-	-	hsa-miR-1281 ↓				
-	-	hsa-miR-6068 ↓				
-	-	hsa-miR-8060 ↓				
-	-	hsa-miR-4433a-5p ↓				
-	-	hsa-miR-1268b ↓				
-	-	hsa-miR-1238-3p ↓				
-	-	hsa-miR-133a-3p ↓				
-	-	hsa-miR-188-5p ↓				
-	-	hsa-miR-6775-5p ↓				
-	-	hsa-miR-6800-3p ↓				
-	-	hsa-miR-3620-5p ↓				
-	-	hsa-miR-5739 ↓				
-	-	hsa-miR-451a ↓				
-	-	hsa-miR-1227-5p ↓				
-	-	hsa-miR-7108-5p ↓				
-	-	hsa-miR-671-5p ↓				
-	-	hsa-miR-6727-5p ↓				
-	-	hsa-miR-6125 ↓				
-	-	hsa-miR-6821-5p ↓				
<i>AP3B1</i>	-	-	Lysosome functioning	<i>USP14</i> ↓	DUB	
<i>TPP1</i>	-	-		-		
<i>CTNS</i>	-	-		-		
<i>CTSK</i>	-	-		-		
<i>AP1S2</i>	-	-		-		
<i>AKTIP</i>	-	-		-		

Note: Data from <sup>31,49,71,73,112,160-165</sup>.

Abbreviations: BD, bipolar disorder; ELAP, endolysosomal and autophagy pathway; MDD, major depressive disorder; UPS, ubiquitin and proteasome system.

A recent review study presented several findings showing autophagic alterations in mood disorders.<sup>55</sup> In animal models, increased expression of the mTOR pathway and decrease of ULK1 protein causes depressive, anhedonia, and anxiety-like behaviors. Moreover, the mTOR is downregulated in both the peripheral blood of depressive BD patients and the PFC of MDD patients. Taken together, these findings suggest that the mTOR pathway could be playing a role in the pathophysiology of mood disorders by regulating the autophagy of cortical neurons.

## Endosomes and Exosomes

Endosomes are sorting compartments that transport proteins throughout the trans-Golgi network.<sup>56</sup> Its functions include recycling and reusing proteins, as well as delivering them to lysosomes for hydrolysis.<sup>56,57</sup> Endosomes are the major vesicles/organelles of the endocytic pathway and are classified as early, recycling, and late endosomes. If the cargo is retained in early endosomes and matures into late endosomes the process is called multivesicular bodies (MVBs).<sup>58</sup> When late endosomes fusions with plasma membranes, vesicles are released into the extracellular environment, these are called exosomes.<sup>59</sup> Studies focusing on endosomes and exosomes in mood disorders are only beginning to emerge, and recent findings require more investigation. Most studies have analyzed either the membrane proteins or the cargo of these vesicles.

A GWAS study<sup>60</sup> of MDD and AD patients found 40 genes that were associated with both disorders, nine of them had already been published as AD risk genes,<sup>61</sup> and out of these nine genes, four are involved in endocytosis (*BINI*, *PICALM*, *SORL1*, and *PTK2B*). This suggests different mental disorders may share the contribution of endocytic pathways in their pathophysiology. Since depressive symptoms can precede clinical manifestations of AD, understanding factors associated with molecules involved in endocytosis might even help in preventing AD later in life.

Cathepsin D is a protease involved in the ELAP as a hydrolase.<sup>62</sup> A recent study conducted in mice model deficient to cathepsin D showed that the animals exhibited anxiety-like, depressive-like behaviors, and mixed manic/depressive-like behavior.<sup>63</sup> This suggests that cathepsin D may be associated with affective symptoms and potentially be an underlying molecular mechanism of mood disorders.

Besides their role in signaling and trafficking of molecules through vesicles, exosomes are also important for quality control of toxic or damaged proteins, lipids, RNAs, and microRNAs (miRNAs),<sup>64</sup> being crucial to cell homeostasis and communication.<sup>65,66</sup> Interestingly, certain molecules belonging to the autophagic machinery were found to contribute to exosome biogenesis.<sup>67</sup>

Once it is challenging to investigate specific molecular alterations in the brains of patients in vivo, the study of brain-derived exosomes allows us to explore alterations in these organelles in the peripheral blood.<sup>68</sup> This is because exosomes exhibit specific proteins in their membrane that end up functioning as markers of the tissue from which they originated. Additionally, exosomes are suggested to be the primary vehicle for miRNA transportation throughout the body.<sup>69</sup> Interestingly, miRNA level alterations are frequently seen in mental disorders.<sup>70</sup>

A recent study focusing on brain-derived exosomes found that several of their miRNAs were differentially expressed in MDD (Table 1).<sup>71</sup> The top differentially expressed exosomal miRNA was the miR-139-5p, which was also altered in brain-derived exosomes of MDD in another study.<sup>72</sup> Interestingly, injection of brain-derived human exosomal miR-139-5p caused depressive-like behaviors in mice models for MDD, while exosomes from healthy patients had antidepressant-like effects.<sup>71</sup> Regarding BD, analysis of plasma exosomes showed thirty-three differentially expressed exosomal miRNAs (Table 1).<sup>73</sup> Among them was miR-29c-3p, a miRNA that had been previously associated with BD.<sup>74</sup> All these findings suggest that peripheral blood and brain exosomes can be biomarkers of mood disorders.<sup>75</sup> Brain-derived exosomes may better correspond to clinical characteristics, since exosomes can cross the blood-brain barrier, which could be reflecting changes in cell communication and targeted cell behavior occurring in the brain.

## Lysosomes

Lysosomes are digestive organelles belonging to the endocytic degradation pathway responsible for finalizing the autophagic process. Lysosomes have also been implicated in mitochondrial stress and mitophagy. Together with mitochondrial stress, the increase of lysosomal biogenesis leads to an increase in mitophagy.<sup>21</sup> There are few studies investigating the role of lysosomes in mood disorders. Since lysosomal storage diseases show psychiatric and behavioral manifestations seen in MDD and BD,<sup>76</sup> studying the role of lysosomal pathway deserves better attention.

Transcriptome analysis of the anterior cingulate showed that among the differentially expressed genes in BD the most enriched pathway was the lysosomal system (genes shown in Table 1).<sup>77</sup> Moreover, depressive-like behaviors are observed in mice models overexpressing acid sphingomyelinase (ASM), a glycoprotein present in lysosomes that act in the catalyzation of hydrolysis.<sup>78</sup> Interestingly, antidepressants seem to downregulate the expression of ASM both in



mice models and non-treated MDD patients.<sup>79</sup> Cathepsins are also involved in mood disorders in the context of lysosomal degradation. Downregulation of cathepsins is frequently seen in BD while their upregulation is associated with depressive-like behavior.<sup>80</sup> These findings suggest further investigation into the role of cathepsins in mood states.

## Ubiquitin and Proteasome System Dysfunction in Mood Disorders

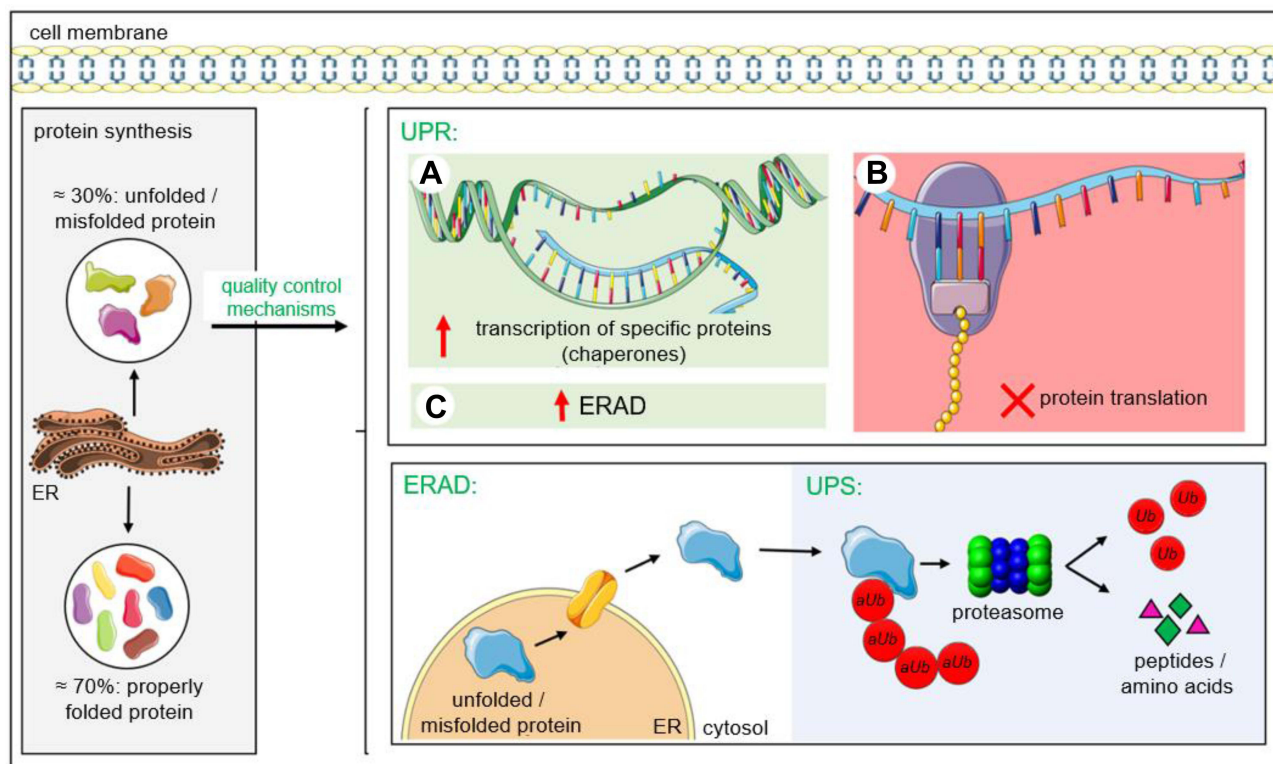
The endoplasmic reticulum (ER) is responsible for the production and folding of proteins, an essential mechanism for proteins to function correctly. However, the formation of poorly folded proteins occurs constitutively in the organism. About 30% of the synthesized proteins do not achieve the appropriate final conformation.<sup>81</sup> Therefore, the protein quality control machinery is present in the ER, comprising the Unfolded Protein Response (UPR), ER-associated degradation (ERAD), and the ubiquitin-proteasome system (UPS)<sup>82,83</sup> (Figure 2).

### Unfolded Protein Response – UPR

The UPR is activated when there is an insufficient capacity to fold proteins, and it acts by increasing the transcription of chaperones (Figure 2A), inhibiting translation (Figure 2B), and positively regulating ERAD components (Figure 2C).<sup>84</sup> Protein synthesis and folding processes depend on appropriate environmental, genetic, and metabolic conditions. When there is a failure in restoring homeostasis, chronic UPR activation occurs, which can induce an apoptotic response.

Oxygen consumption in the brain is high and consequently, ROS production and oxidative stress are increased when compared to other organs. Oxidative stress is one of the factors responsible for protein malformation and requires the activation of UPR.<sup>85</sup> Interestingly, evidence has suggested that UPR dysfunction may be involved in MDD, and BD.<sup>86</sup> Several studies showed the implication of UPR in mood disorders (Figure 3).

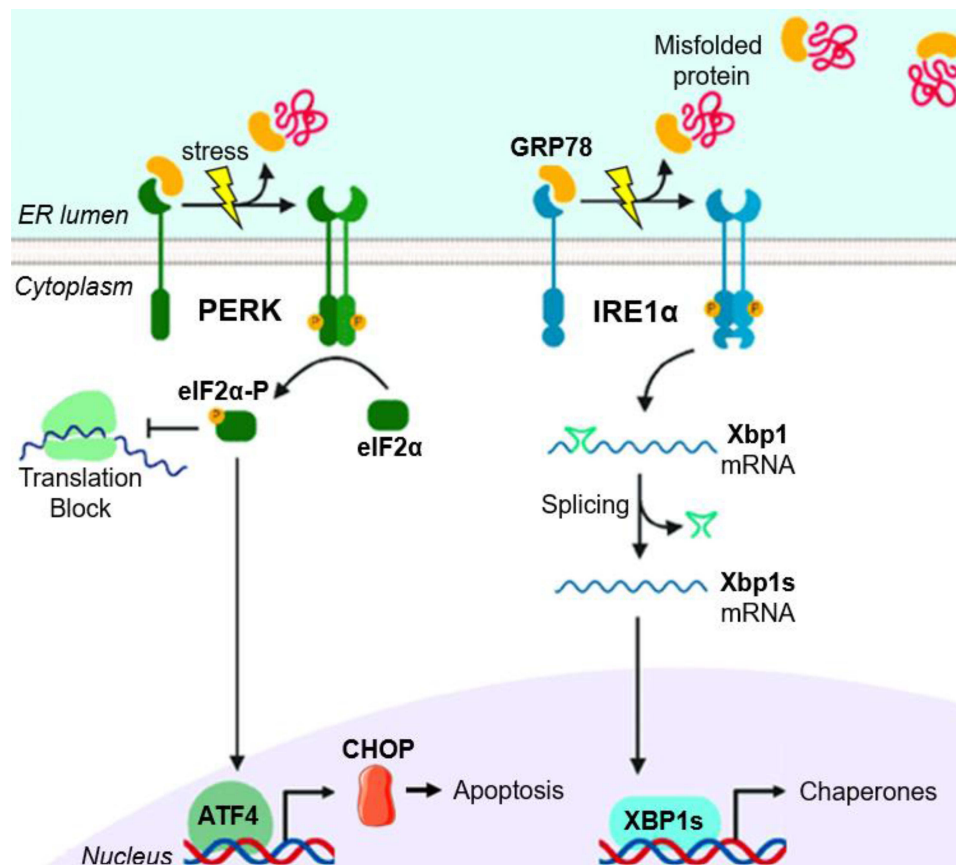
Lymphocytes from individuals with BD subjected to stress did not show variation in the levels of GRP78 protein nor phosphorylation of eIF2 $\alpha$  initiation factor or CHOP protein, which suggests that they present inherent a priori



**Figure 2** Protein quality control systems are activated upon the occurrence of unfolded proteins. The UPR acts in three ways: (A) increasing the transcription of chaperones; (B) inhibiting translation; (C) positively regulating ERAD components.

**Abbreviations:** ERAD, ER-associated degradation; UPR, Unfolded protein response; UPS, Ubiquitin–proteasome system; aUb, Ubiquitin activated; Ub, Ubiquitin.





**Figure 3** UPR's mechanisms of action. In stress situations, PERK and IRE1 $\alpha$  proteins dissociate from the GRP78 chaperone, autophosphorylates, form dimers, and phosphorylate other proteins. PERK phosphorylates eIF2- $\alpha$ , causing attenuation of protein translation. When the levels of eIF2- $\alpha$  are limited, ATF4 mRNA is translated and up-regulates CHOP, which responds to induce apoptosis. IRE1 $\alpha$  activates XBP1 mRNA splicing, thus inducing the expression of chaperones.

**Note:** Flores-Santibáñez F, Medel B, Bernal JI, Osorio F. Understanding the Role of the Unfolded Protein Response Sensor IRE1 in the Biology of Antigen Presenting Cells. *Cells*. 2019 Dec 4;8(12):1563. doi: 10.3390/cells8121563. <http://creativecommons.org/licenses/by/4.0/>.

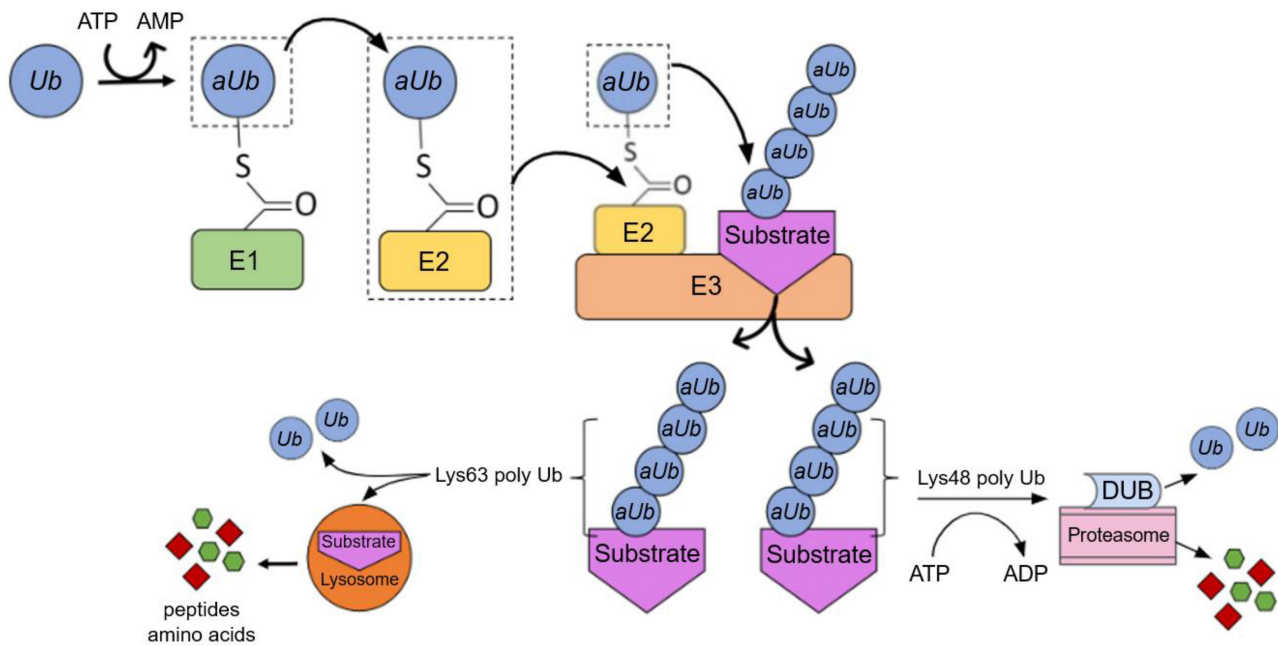
**Abbreviations:** PERK, protein kinase-like endoplasmic reticulum kinase; IRE1 $\alpha$ , inositol requiring enzyme 1 $\alpha$ ; GRP78, glucose-regulated protein 78; eIF2- $\alpha$ , eukaryotic initiation factor 2 alpha; eIF2 $\alpha$ -P, phosphorylation of eukaryotic initiation factor 2 alpha; XBP1, x-box binding protein 1; XBP1s, spliced form of XBP1; CHOP, C/EBP homologous protein; ATF4, activating transcription factor 4.

dysfunction in stress-response.<sup>87</sup> Furthermore, lymphocytes in the BD group demonstrated significant cell death suggesting that UPR-induced apoptosis may reestablish homeostasis. Interestingly, when patients were divided considering disease chronicity, only patients in early stages submitted to prolonged stress and with advanced-stage BD did not present UPR modulation, showing that UPR dysfunction may be associated with decreased resilience and, consequently, the progression of the disease.<sup>87</sup> Genetic studies corroborate the hypothesis that UPR is involved in the pathophysiology of BD since an association was observed between this disorder and polymorphisms in the promoter regions of the genes *GRP78*<sup>88</sup> and *XBP1*.<sup>89</sup> Furthermore, the expression of *XBP1* was significantly decreased in the peripheral blood of BD.<sup>90</sup>

In MDD, mRNA levels of *GRP78*, *GRP79*, and *ATF4C* transcription factors were elevated in individuals with the disorder who died from suicide.<sup>91</sup> This suggests that UPR mediation may be a critical factor for suicide among subjects with MDD.<sup>91</sup> Taken together, we hypothesize that UPR alterations could be a molecular mediator of stress response caused by environmental modifications, often experienced by mood disorder patients.

## Ubiquitin-Proteasome System – UPS

The UPS is the main pathway of protein degradation in eukaryotes. Through this pathway, ubiquitin marks misfolded or damaged proteins in a process named ubiquitination.<sup>92</sup> This process is performed by ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3)<sup>93</sup> (Figure 4) and serves as a signal for degradation.



**Figure 4** The ubiquitin-proteasome pathway. The ubiquitin (Ub) binds to E1, and it is activated (aUb). Then it is transferred to E2. The complex (E2 + aUb) binds to E3 and then aUb connects to the target protein. Other monomers bind to aUb, forming a polyubiquitinated chain, which serves as a signal for degradation. If the linkage involves lysine-63, degradation occurs through the lysosome, whereas if the linkage involves lysine-48, degradation is dependent on the 26S proteasome. The deubiquitination enzymes (DUBs) remove the substrate from the protein, before being degraded.

Ubiquitinated proteins will be targeted to the proteasome for proteolysis. The ubiquitination process is reversible and regulated by deubiquitinating enzymes (DUB), which remove ubiquitin from the substrate before it is degraded (Figure 4).

UPS is involved in the development and neuronal function and in cell signaling during stress, inflammation, and apoptosis.<sup>94,95</sup> For this reason, many studies have associated UPS and mood disorders.<sup>96,97</sup>

The E3 play a critical role in the selectivity of substrates, which acts in maintenance of synaptic plasticity and transmission, remodeling of the dendritic column, as well as in the regulation of neurotransmitters receptors.<sup>98–100</sup> In an animal study, both mRNA and protein levels of the E3 Nedd41 were increased on the medial PFC (mPFC) of mice susceptible to stress as well as the ubiquitination of the neurotrophin neuregulin (NRG1).<sup>101</sup> This suggests that NRG1 is ubiquitinated by Nedd41 and that this ubiquitination regulates its levels. These findings are relevant in the context of mood disorders since NRG1 regulates processes of neuronal development, such as synaptic plasticity.<sup>102</sup> Brain-derived neurotrophic factor (BDNF), which is another neurotrophin involved in MDD,<sup>103</sup> has its expression mediated by an E3 substrate (Pdc4). Exposure to chronic restriction stress decreases the ubiquitination of Pdc4, resulting on its overexpression causing a decrease in BDNF levels in the hippocampus of mice.<sup>104</sup> Despite the well-known changes in BDNF expression in MDD, its regulation by UPS is a new perspective.

These findings suggest that environmental stressors could promote alterations in the functioning of the UPS pathway, which could result in dysfunctional behavioral phenotypes. Aberrant regulation of neuronal plasticity may result in structural changes that contribute to the pathophysiology of MDD.<sup>105</sup> Neuroimaging studies have shown that depressed patients have a reduced volume of the mPFC and hippocampus<sup>106</sup> and postmortem studies have revealed a significant decrease in the number of synapses in the PFC.<sup>107</sup> It is known that exposure to stress leads to a decrease in neurotrophic factors, atrophy, and cell loss in the hippocampus.<sup>105</sup> We hypothesize that changes in UPS components could be participating in stress-induced neurochemical and structural changes in mood disorders.

Different studies that sought to understand the antidepressant response and find biomarkers for clinical outcomes demonstrated that ubiquitin ligases are associated with therapeutic efficiency.<sup>108–110</sup> The intergenic variant rs6916777, mapped to the RNF217 gene/protein (an E3), was associated with a better response to venlafaxine in a study of GWAS in depressive elderly patients.<sup>109</sup> Another gene expression evaluation was performed in rats submitted to maternal separation and three proteins involved in ubiquitination (Herc6, Asb5, Rnf7) were associated with the antidepressant response.<sup>108</sup>

Investigation of peripheral blood mononuclear cell methylome from depressed patients undergoing electroconvulsive therapy (ECT) revealed that, out of five genes implicated in the ECT response, two (RNF175 and RNF213) encode ubiquitin ligases.<sup>110</sup> Considering that a significant proportion of patients with MDD do not achieve remission with pharmacotherapy or ECT,<sup>111</sup> the findings presented here are relevant, since they can help in the identification of new treatment approaches.

In addition to the important role of E3 in mood disorder, a meta-analysis of risk genes for MDD identified UBE2M (coding for an E2) as one of the genes with the most consistent differential expression (Table 1).<sup>112</sup> In BD, studies have shown that E2 and E3 may be involved in the pathophysiology of the disorder.<sup>113,114</sup> UBE3A and CUL1 genes (coding for E3) are negatively expressed in the frontal cortex of BD subjects.<sup>114</sup> Valproic acid, frequently used as an antimanic agent in BD can induce differential expression of *ANAPC4*, *CDC23*, *FBXO2*, *FBXO4*, *NEDD4*, *TRAF6*, *UBE2D1*, *UBE2E1*, *UBE2E3* and *UBE2G2*, genes encoding E2 and E3<sup>113</sup> in human neuroblastoma cells.

Genes encoding proteasome subunits (*PSMD2*, *PSMD6*, *PSMA1*, *PSMB8*, and *PSMB9*) are differentially expressed in the umbilical cord of newborns of mothers exposed to MDD.<sup>115</sup> A proteomic analysis of the PFC of rats found that chronic social isolation negatively regulated Psmb7, Psmb3, Psmb2, Psmb6, Psma6 and Psmb4, which are cytosolic proteasomal proteins.<sup>116</sup> The authors suggested that these proteins have been proposed as potential markers of depression induced by environmental stressors. Interestingly, a GWAS study reported an upregulation of several proteasome-related genes in MDD as one of the most robust results.<sup>117</sup> Taken together the results indicate the hypothesis that dysregulation of proteasomal subunits contributes to the expression of the depressive phenotype. Finally, the *PSMD13* rs3817629 G allele (a subunit of the proteasome) was associated with an increased risk of developing treatment-resistant depression.<sup>118</sup> Furthermore, expression of this genotype was associated with reduced transcription of *PSMD13* in fibroblasts from MDD patients.<sup>118</sup>

The function of DUBs as ubiquitination antagonists is equally important. These specific enzymes, which regulate multiple cellular processes, have been implicated in MDD and BD.<sup>119,120</sup> The *USP46* gene (DUB encoding) was identified as responsible for depressive-like behavior in mice.<sup>119</sup> The lack of expression of *USP46* showed antidepressant effects.<sup>121</sup> A study in humans demonstrated significant differences in *USP46* single nucleotide polymorphisms between MDD patients and controls.<sup>122</sup> Recently a study found that the CC genotype of *USP46* rs346005 is related to a higher depressive temperament score in males,<sup>123</sup> which are risk factors for suicide in mental disorders.<sup>124</sup>

One of the most recent large-scale GWAS studies included 41,917 confirmed *ANK3* as the main locus of risk for BD.<sup>125</sup> *ANK3* encodes ankyrin-G, which acts in processes such as synaptogenesis, synaptic plasticity, action potential generation and transmission, and ion channel regulation.<sup>126–128</sup> Recently, it was found that ankyrin-G is controlled by *USP9X* (a DUB) and that this process is essential for the development of the dendritic column.<sup>120</sup> *USP9X* knockout mice show reduced levels of ankyrin-G, which are recovered 12 weeks after birth.<sup>120</sup> However, these mice had a reduction in cortical spine density, which persisted into adulthood.<sup>120</sup> This reveals that although protein levels are transiently affected, behavioral and clinical dysfunctions are persistent. To date, there are no studies investigating the functioning of *USP9X* in BD, despite the *ANK3* gene variants being among the risk factors most strongly associated with this disorder. Whereas a high expression of the *ANK3* isoform in BD<sup>129</sup> and a significant reduction in the density of the dendritic column in the dlPFC of individuals with BD<sup>130</sup> were observed, investigating the expression/function of *USP9X* in BD patients may provide relevant insights into the mechanisms underlying the disorder and possible alternative therapeutic approaches.

## Targeting Endo-Lysosomal/Autophagy and Ubiquitin/Proteasome Pathways: Translating Basic Findings to Clinical Practice

### Endo-Lysosomal and Autophagy Pathways

Synthetic biology is an emerging technology that can be applied for therapeutic purposes using gene circuits to change cellular behavior.<sup>131</sup> There are several potential ways of using synthetic biology for therapeutic capabilities, one of them is building models to sense the expression of endogenous miRNAs as biomarkers.<sup>132,133</sup> Additionally, miRNAs can also be used as inputs to gene circuits triggering changes in cellular responses. miRNA has been used as biomarkers in synthetic circuitry to induce apoptosis in cancer cells.<sup>134,135</sup> Since alterations in the expression of specific miRNAs are observed in BD (miR-29c-3p) and MDD (miR-139-5p), this strategy could be used to regulate cellular behavior in mood

disorders.<sup>71,73</sup> Given that miRNAs are present in exosomes of BD and MDD, validating these molecules as biomarkers for these disorders could be a starting point for the use of synthetic biology in mood disorders. Once robust findings on miRNAs as biomarkers of mood disorders have been established, these molecules could be used to activate gene circuitry (ie, TSPO) to promote specific cellular responses (ie, mitophagy) in BD, for example. This idea could be applied to other target molecules within the ELAP or UPS (for example the ones cited in Table 1). Preclinical strategies, such as the use of synthetic biology in iPSC of mood disorder patients may bring insights to further clinical applications.

Recently, targeted degradation has emerged as a promising therapeutic strategy.<sup>136</sup> Lysosomal-targeting chimeras (LYTACS) and autophagy-targeting chimeras (AUTACS) use targeted degradation and explore ELAP and autophagic degradation pathways.<sup>136</sup> AUTACS are heterobifunctional compounds, which contain guanine derivatives, which function as a tag for autophagic degradation, connected to a specific ligand of an intracellular target.<sup>137</sup> On the other hand, LYTACS are intended for membrane-bound and extracellular proteins. In this sense, LYTACS are composed of two domains, one of which is an extracellular/membrane-bound protein binding element and the other a chemically synthesized glycopeptide whose function is to transport this target substrate to the lysosome.<sup>138</sup>

In addition to targeting proteins to autophagy, AUTACs have also been shown to target mitochondria to mitophagy. Mitochondrial dysfunctions have been associated with the severity and progression of BD and MDD,<sup>24,42</sup> which causes cellular toxicity, and vulnerability to future episodes.<sup>139</sup> Therefore, ensuring the maintenance of cellular resilience is a strategy to increase neuroprotection. In this context, treatment with mitochondria-targeted AUTACs (mito-AUTAC) may bring a possibility of novel adjunctive therapies for maintaining cellular resilience in mood disorders. In Down's syndrome, a cell culture study showed that treatment with mito-AUTAC accelerated the removal of dysfunctional fragmented mitochondria, as well as the biogenesis of fully functioning mitochondria.<sup>137</sup>

## Ubiquitin Proteasome System

Stimulation of neuronal plasticity via the UPS could also be a way of promoting neuroprotection in mood disorders as an adjunctive therapy. Neuronal plasticity allows for the readaptation of brain networks under stress conditions.<sup>140</sup> BDNF-mediated plasticity is one of the mechanisms responsible for the clinical effects of antidepressants.<sup>140</sup> Modulating BDNF levels by increasing the ubiquitination of Pcd4 may be one considerable strategy. Studies have shown that other types of E3 ligase, such as TRIM27<sup>141</sup> and  $\beta$ TRCP<sup>142,143</sup> can regulate Pcd4 expression by inducing its degradation via UPS. Therefore, studies investigating the specificity of these E3 and whether their expression in the hippocampus can promote antidepressant effects are necessary.

Stimulation of plasticity through UPS could also be mediated by the BDNF receptor TRKB. Recent studies have found that antidepressants bind directly to TRKB facilitating its location on the synaptic surface and signaling.<sup>144</sup> In addition to being phosphorylated, TRKB can also be ubiquitinated and deubiquitination altering its biological functions.<sup>145,146</sup> Recently it was shown that USP8 (a DUB) binds to the TRKB receptor and upregulates its levels and activation.<sup>146</sup> Post-mortem studies have demonstrated the decreased expression of TRKB in different brain areas of suicidal individuals.<sup>147,148</sup> Therefore, regulating the expression and activation of TRKB through DUBs could be a promising treatment strategy, and studies evaluating the feasibility of such an application are required.

Besides the reduced neuroprotection that underlies the pathophysiology of mood disorders, inflammation is also a biological substrate of these disorders.<sup>149</sup> Lithium, the drug most recommended for the treatment of BD, is a GSK-3 $\beta$  inhibitor.<sup>150</sup> GSK-3 $\beta$  promotes the production of inflammatory molecules, which can cause neuronal loss.<sup>151</sup> The effectiveness of lithium for the treatment of BD is fully recognized.<sup>152</sup> Likewise, potential side effects and risks associated with lithium long-term use are also well known,<sup>152</sup> but often overlooked. Studies that investigate new therapies aiming not only for a better understanding of the efficacy but also the tolerability of the pharmacological treatments are necessary. In this context, proteolysis targeting chimeras (PROTACs) emerge as a promising alternative. PROTACs are a new technology that utilizes UPS to achieve target protein degradation.<sup>153</sup> These are micromolecules, hetero-bifunctional, composed of two interconnected active domains. One of the domains binds to the target protein and the other to the E3 ligase. In this way, PROTACs bring the ubiquitination machinery closer to the target protein and initiate the degradation cascade, finally directing the proteins to the proteasome for proteolysis.<sup>153</sup> Recently, the first PROTAC capable of degrading the GSK-3 $\beta$  protein (PG21) has been developed.<sup>150</sup> Its synthesis was based on an E3 ubiquitin, ligase cereblon.<sup>150</sup> Considering that



lithium and PG21 exert the same activity (inhibit GSK-3 $\beta$ ), we suggest that this PROTAC could be an alternative drug for BD therapy. In addition, PROTACS have high specificity, which favors the treatment of chronic diseases such as BD, since it makes it possible to reduce the frequency of administration.<sup>153</sup> Therefore, studies aiming to better understand the potential therapeutic effects of PG21 in mood disorders (especially BD) are needed.

On the other hand, diseases can also be caused by excessive protein ubiquitination and degradation.<sup>154</sup> In this sense, the use of deubiquitinase targeting chimeras (DUBTACS) could be an alternative. DUBTACS are also heterobifunctional molecules composed of two interconnected domains, but one of the domains corresponds to a DUB recruiter and the other to a ligand directed to target proteins.<sup>154</sup> In this way, a DUBTAC brings a DUB closer to a target protein, which results in the removal of ubiquitin chains, that is, in deubiquitination, which rescues the protein from degradation, leading to an increase in protein levels and stability.<sup>154</sup>

Currently, several PROTACs have been used in clinical trials.<sup>155</sup> In these trials, two oral PROTACs (ARV-110 and ARV-471) were shown to be effective in the treatment of prostate and breast cancer.<sup>155</sup> There are still no clinical trials involving DUBTACs. This technology is very recent, the first DUBTAC was developed in 2022.<sup>154</sup> DUBTACs have been suggested to stabilize tumor suppressors, which are ubiquitinated and degraded in disease, maintaining cancer cell proliferation.<sup>154</sup> In summary, both PROTACs and DUBTACs have cancer-oriented applications that extensively foster research and development in academia and pharmaceuticals. Given the fact that several studies have shown the impact of UPS in mood disorders, these new technologies (PROTACs and DUBTACs) can be applied to BD and MDD as well. In the case of DUBTACs, they could maintain cellular resilience by inducing apoptosis of dysfunctional mitochondria, through the stabilization of BAX levels (pro-apoptotic).<sup>156</sup> Furthermore, this technology could be considered to recruit USP8 to stabilize TRKB, which is decreased in MDD patients.<sup>147</sup>

## Conclusions and Future Directions

We reviewed the findings on the role of different molecules belonging to the ELAP and UPS in mood disorders. Current findings on this field suggest further investigation on the role of TSPO in regulating mitophagy in BD and mTOR in autophagy in BD and MDD. Concerning the UPS attention should be given to the potential of E3 and DUBs in mediated neuroprotection in both BD and MDD. The fact that most of the molecular alterations in these pathways were observed in the frontal cortex and that this brain region is involved in the pathophysiology of BD and MDD suggests that these pathways may be underlying the brain circuitry dysfunction seen in these disorders.<sup>157,158</sup>

Based on the literature review, we sought to bring into discussion potential translational strategies that could improve the diagnosis and treatment of mood disorders. Further characterizing miRNA contained in the brain-derived exosomes may inform more robust biomarkers with clinical meaning. Additionally, a better characterization of the miRNAs related to BD and MDD may open the possibility of applying synthetic biology to translational purposes in mood disorders. Once synthetic biology acts on specific biomarkers and gene circuits to change cellular behavior, this technology could be applied in the context of personalized medicine in subsets of patients showing common clinical phenotypes in the future. Furthermore, AUTACs, mito-AUTACS, LYTACS, PROTACS, and DUBTACS achieve targeted and selective degradation of proteins, including targets previously considered “non-druggable”.<sup>159</sup> These strategies could act on molecules underlying the ELAP and UPS found in BD and MDD and bring new therapeutic perspectives to these mood disorders.

## Abbreviations

AD, Alzheimer’s disease; ASM, acid sphingomyelinase; AUTACS, autophagy-targeting chimeras; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; DIPFC, dorsolateral prefrontal cortex; DUB, deubiquitinating enzymes; DUBTACS, deubiquitinase-targeting chimeras; ELAP, endolysosomal and autophagy pathway; ER, endoplasmic reticulum; ERAD, ER-associated degradation; ETC, electroconvulsive therapy; E1, ubiquitin-activating enzymes; E2, ubiquitin-conjugating enzymes; E3, ubiquitin ligases; GWAS, genome-wide association studies; iPSCs, induced pluripotent cells; LYTACS, lysosomal-targeting chimeras; MDD, major depressive disorder; mito-AUTAC, mitochondria-targeted AUTACs; mPFC, medial prefrontal cortex; miRNAs, microRNAs; mTOR, mammalian target of rapamycin; MVBs, multivesicular bodies; NDDs, neurodegenerative diseases; NRG1, neuregulin; PFC, prefrontal cortex; PROTACS,

proteolysis-targeting chimeras; ROS, reactive oxygen species; SS, susceptible to stress; UPR, unfolded protein response; UPS, ubiquitin-proteasome system.

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## Disclosure

The authors report no conflicts of interest in this work.

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