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INVITED REVIEW

Psychiatric disorders biochemical pathways unraveled by human brain proteomics

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Abstract Approximately 25 % of the world population is affected by a mental disorder at some point in their life. Yet, only in the mid-twentieth century a biological cause has been proposed for these diseases. Since then, several studies have been conducted toward a better comprehension of those disorders, and although a strong genetic influence was revealed, the role of these genes in disease mechanism is still unclear. This led most recent studies to focus on the molecular basis of mental disorders. One line of investigation that has risen in the post-genomic era is proteomics, due to its power of revealing proteins and biochemical pathways associated with biological systems. Therefore, this review compiled and analyzed data of differentially expressed proteins, which were found in postmortem brain studies of the three most prevalent psychiatric diseases: schizophrenia, bipolar disorder and major depressive disorders. Overviewing both the proteomic methods used in postmortem brain studies, the most consistent metabolic pathways found altered in these diseases. We have unraveled those disorders share about 21 % of proteins affected, and though most are related to energy metabolism pathways deregulation, the main differences found are 14-3-3-mediated signaling in schizophrenia, mitochondrial dysfunction in bipolar disorder and oxidative phosphorylation in depression.

Keywords Proteome · Mass spectrometry-based proteomics · Schizophrenia · Bipolar disorder · Major depressive disorder · Postmortem brain

Introduction

Since ancient Egypt, mankind attempts to understand mental illness, however, only around the mid-twentieth century, a probable biological cause was confirmed. Since then, modern psychiatry has established a set of systematic criteria for diagnosis, psychological therapies and the development of new drugs. And despite all progress, the prevalence of neuropsychiatric disorders has not diminished. Strong genetic influence of these diseases has been elucidated, yet the role of such genes is still unclear [1]. Hence, more detailed molecular-based studies are necessary for a better understanding of mental disorders. Approximately 25 % of the world population will, at some point in their lifetime, be affected by a mental disorder [2]. Among the leading causes of disability, especially among woman between 15 and 44 years old, there are several mental disorders, of which five of these disorders are listed as the first cause of burden, schizophrenia as the fifth and bipolar disorder as the seventh [3]. These diseases cause an increased risk of additional health problems, premature death, in addition to suicide attempts [4, 5].

The burden of mental disorders

Currently, depressive disorders are the most common mental illnesses worldwide, estimated to affect about 350

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million people of all ages [3]. Major depressive disorder (MDD) is associated with high health costs [6], and according to the National Comorbidity Survey (NCS) it has a prevalence of 14.4 % over lifetime and 7.1 % on a 12-month period [7]. The main symptoms of this disease are depressed mood and/or loss of interest or pleasure [8], while secondary symptoms are change in sleep, appetite, fatigue/energy loss, feelings of worthlessness or guilt, diminished concentration and suicidal thoughts [8, 9]. The basis for MDD treatment still consists in antidepressants, and only 30–40 % of the patients satisfactorily respond to them [10, 11]. There are several hypotheses aiming to explain the molecular basis of MDD; however, the pathophysiology of these diseases is only partially understood [12–14].

Schizophrenia (SCZ) is a chronic mental disorder that usually emerges at the end of adolescence and develops slowly for months or even years [15]. SCZ may affect up to 1 % of the world population and presents a hereditability of 80–85 % [16], which may cause a lifespan reduction in almost 20 years [17]. A burden that displays different symptoms, which are classified as positive, such as hallucinations, deliria and thought disorders, and as negative, such as social interaction disorders, lack of motivation and anhedonia. Furthermore, cognitive deficiencies, such as the reduction in executive functions, selective attention, working memory and mental flexibility, may also be present [18]. As a multifactorial disease, SCZ involves exogenous and endogenous factors since the beginning of neurodevelopment [19]. Some of the molecular aspects of SCZ are still to be unraveled, while the connection among the known aspects has still to be improved toward a more integrated understanding of its physiopathology.

Bipolar disorder (BPD) is another psychiatric disorder that may affect up to 4 % of the world adult population [20]. It is characterized by two well-defined mood shifts, from manic to depressive mood, and it is possible to have periods with symptoms from both states. The diagnosis of BPD is performed clinically. This is a challenge, since the disease has a great heterogeneity, with unclear limits when compared to other psychiatric disorders [21]. Lithium is by far the most commonly used drug for BPD and works as a mood-stabilizing agent; nevertheless, its specific way of action was not yet entirely unraveled. However, there are several theories trying to explain its action mechanism, such as ionic channel alterations, or gene expression modulation [21–23]. A cause factor for BPD remains unknown, what is already known is that some biochemical, genetic and environmental disturbed patterns may trigger the disease.

The study of the brain is the most natural way to understand these neuropathologies, aiming to find possible causes for those brain disorders [24]. In addition, cellular and molecular arrangements differ between brain regions; thus, a better comprehension arises from characterizing them at the molecular level and their correlation with the disease pathobiology. Hence, this review aims to evaluate and connect proteomic studies of human brain from patients with SCZ, MDD and BPD, in order to better understand those diseases. These studies employed a myriad of proteomic techniques, which are described in detail below.

Proteomic methods used in neuropsychiatric studies

2DE/2D-DIGE

The pioneer technique employed not only in psychiatric studies, but also in proteomic investigations in general, was the two-dimensional electrophoresis (2DE) [25]. Since the 1970s, when developed [25], this technique is widely used in proteomic studies. Hence, between 2000 and 2010 half of the articles in proteomics in PubMed employed 2DE as its main method of study [26], which is still used for some particular questions, such as the study of intact proteins [26]. The 2DE combines two techniques: isoelectric focusing (IEF), followed by a separation by SDS-PAGE. Therefore, as all techniques of electrophoretic separation, molecules with charge migrate under the influence of an electric field, and their migration velocity will depend on specific features of these molecules, such as size, shape and electrical charge.

Thus, by late 1990s this technique was powered by the development of differential two-dimensional electrophoresis (2D-DIGE) [27]. Herein, proteins are covalently labeled in their lysine residues with fluorescent cyanins (-Cy3, Cy5 and Cy2), and the samples are mixed prior to electrophoretic separation, enabling precise and more sensitive proteome quantification. Consequently, increasing reproducibility and sensitivity, samples can be compared in a single gel [28]. Inherent limitations of 2DE, which also applies to 2D-DIGE, are the difficulty of separating hydrophobic and extremely acidic or basic proteins, which can be partially solved by protein extraction methods using detergents. Moreover, proteins larger than 150 kDa and smaller than 10 kDa can be missed, demanding experiments using several gels with variable acrylamide concentrations. Computational analyses of gels are rather semi-automated, demanding manual corrections for the quantification of protein expression.

Even with all limitations, 2DE and 2D-DIGE are genuinely a top-down analytical approach [26]. Their resolution power is remarkable as they are capable of resolving more than 10,000 protein spots in a single run [29], besides resolving protein isoforms and posttranslational modifications.

But their application to proteomics heavily relies on mass spectrometry for the identification of proteins.

Mass spectrometry-based proteomics

A combination of liquid chromatography and mass spectrometry used for large-scale proteome analysis became popular by the end of the 1990s, when the term "Shotgun Proteomics" was coined [30]. At that point, shotgun proteomics could be simply referred as mass spectrometry-based proteomics. But considering all the recent developments, both terms are actually referring to "mass spectrometry-based bottom-up proteomics." This consists primarily of the analysis of a digested proteome, which undergoes a chromatographic separation followed by MS/MS analysis [31, 32]. Although this is virtually impossible, the aim here is to unveil the whole proteome of a given sample. For that, depending on the sample analyzed, single liquid chromatography could be insufficient to resolve the complexity of biological protein mixtures, requiring a multidimensional chromatography separation. This concept has been applied since the description of MudPIT (multidimensional protein identification technology) in 2001 [33], but only more recently multidimensional chromatography separation has been more often used by a significant number of proteomic studies [34, 35]. A given 2D-LC system may employ, for instance, a first separation of peptides by strong cation exchange (SCX) or by reversed-phase column, and this last has recently been more used, followed by separation on a reversed-phase column (RP), which could be employed.

Mass spectrometry-based quantitative proteomics

In recent years, mass spectrometry-based quantitative proteomics has earned significant space among quantitative techniques for proteins [36]. It is an alternative for antibody-based protein analysis, as virtually any protein can be accurately measured in a large number of samples [37].

Stable isotope/isobaric labeling approaches

Quantification of proteins is a key aspect in proteomic studies. Efforts in developing effective methods to increase sensitivity and accuracy led to the development of stable chemical (e.g., ICAT, iTRAQ, ICPL and TMT) and metabolic (SILAC, SILAM and ^{15}N) labeling techniques. Isotope-coded affinity tags (ICATs) were the first application of stable isotope labeling to quantitative proteomics [38]. It relies on heavy and light mass tags containing either eight or no deuterium atoms, respectively, allowing the comparison of two samples in one experiment. Isotope-coded protein label (ICPL) follows the same principle, but up to 4 samples could be labeled at once [39].

Isobaric tags for relative and absolute quantification (iTRAQ) are one the most used in vitro labeling technique in proteomic studies. Quantification consists of different isobaric tags, which label up to eight different samples, and can be used in any biological system [40]. Proteolytic peptides of each sample are labeled with an iTRAQ specific tag, and then, samples are mixed and further analyzed in LC–MS/MS [40]. iTRAQ tags present three distinct regions: one that reacts with the peptide, a reporter region, and a balance that complements the reporter region mass, making iTRAQ tags isobaric [41]. Once a given labeled peptide is submitted to MS/MS, the balance and reporter break apart, and the masses of the reporters are measured. The intensity of these reporters is linearly correlated with the quantity of the given peptide.

In addition, among metabolic labeling techniques, stable isotope labeling by amino acids in cell culture (SILAC) is the most employed and relies on the incorporation of non-radioactive, stable isotope containing amino acids in newly synthesized proteins. Culture medium is supplemented with "heavy" amino acids instead of natural amino acids to be incorporated into proteins. Then, both light and heavy-treated cells are mixed and processed together, until analysis by LC–MS/MS, when labeled peptides can be distinguished, and therefore, abundance was determined by relative signal intensities [42].

Label-free

On the other hand, there are label-free approaches, which are simpler, require no additional wet-lab experiments and are reproducible and cheaper compared to stable isotope labeling techniques [43]. However, label-free quantification requires hard and specialized in silico analysis, thus turning relative quantification possible [44–46]. Label-free quantitative analysis is based on two main approaches, the first is to count and compare fragment ion in spectra acquired from peptide derived from a precursor protein [47, 48]. The second parameter is the measurement of the chromatographic peaks' areas of peptide precursor ions, which is possible since these peaks are supposed to have a linear correlation with the amount of protein present in the sample [49]. In addition, label-free quantification does not limit the number of samples and conditions to be compared, which is suitable to longitudinal and clinical proteomics [50].

Targeted proteomics

SRM

Selected/multiple reaction monitoring (SRM/MRM) is able to detect and perform accurate quantitation of a target protein, or set of proteins, present in complex biological

samples [51]. This technique is performed with high efficiency in triple quadrupole mass spectrometers (TQ or QqQ), wherein the first analyzer (Q1) achieves the isolation of a given intact peptide (parent ion); the second analyzer (Q2, which is not a proper quadrupole in current mass spectrometers) works as a collision chamber, generating fragments (daughter ions) that will be measured separately and accurately in the third quadrupole (Q3). The various transitions between the precursor and fragment ion pairs are monitored over time, and when combined with standard chromatogram, peak retention time and intensity produce a high selectivity for quantification [52–55].

More recently, targeted-MS has been also employed in Q-TOF and Orbitrap mass spectrometers. The latest performs the so-called parallel reaction monitoring (PRM), which measures daughter ions on a HR/AM mass analyzer instead of a quadrupole. This allows the parallel detection of all daughter ions from a given parent ion at once [56, 57]. PRM offers alternative ways to conduct targeted proteomics studies with comparable performance as SRM [58]. In a recent study, this type of acquisition was also implemented in an instrument of the type quadrupole time of flight (QqTOF). Using complex biological samples, selectivity and reproducibility of PRM compared to SRM were evaluated, showing a satisfactory performance of this instrument using this technique [59].

Antibody-based techniques

Immunoassays have been the basis for protein measurement for over half a century, with a limited range of tests available mainly for diagnosis [60]. Historically, Western blotting is the most common technique for immunodetection of proteins in complex samples. It consists basically in the transference of proteins from a gel to a membrane where the specific protein labeling with the respective antibodies will be performed [61]. Alternatively, commercially available enzyme-linked immunosorbent assay (ELISA) can be more sensitive if compared to Western blot, in addition to better relative quantification using recombinant proteins [62].

Western blot and ELISA are both commonly used in proteomics as validation tools for differences in protein expression. The major drawback is that these techniques depend on specific and well-characterized antibodies, which can be challenging, especially for the study of posttranslational modifications. More recently, an analysis of large-scale antibody-based proteomic technique has emerged. Though using a lower throughput compared to mass spectrometry, this analysis employs multiplexed dye-coded microspheres, coated with antibodies. Those microspheres are used for identification and quantification of hundreds of proteins simultaneously, depending on the antibody composition of the assay, in dozens of individual samples [63]. The amount of sample required is also an advantage compared to other antibody-based techniques, though it still depends on the quality of those for greater reproducibility [64–68].

Biochemical pathways associated with neuropsychiatric disorders unraveled by proteomics

This review analyzes every proteomics study published thus far in several postmortem brain regions of patients with schizophrenia (SCZ), bipolar disorder (BPD) and major depression disorder (MDD). All differentially expressed proteins found in these studies were computed. The survey was conducted in PubMed with the following keywords "proteomic/proteome brain and schizophrenia/bipolar disorder/major depressive disorder," We found 14 articles on SCZ studies [69–83], 4 on BPD [82, 84, 85] and 7 on MDD [69, 79, 86–88], which found up- and down-regulated proteins that were compiled and are presented in Supplementary table 1. BPD studies unraveled 731 differentially expressed proteins, while 412 proteins were discovered in SCZ studies and 187 proteins in MDD. All these proteins were further analyzed only by Ingenuity Pathway Analysis software (IPA, Ingenuity Systems, QIAGEN, Redwood, CA, USA; www.ingenuity.com), using curated connectivity information from the literature to determine interactions network among differentially expressed proteins and determine canonical pathways in which they are involved [89]. Parameters used in the IPA software were: "genes only," "include direct and indirect relationship" and "do not include endogenous chemicals." Only molecules and/or relationships in humans were considered, and all cell types/tissues were taken into account, using prediction mode assigned to experimentally observed OR high.

Similarities among disorders

We compared the similarities of differentially expressed proteins associated with SCZ, MDD and BPD and found a small overlap among them (Fig. 1). About 26 proteins are common among SCZ, MDD and BPD; additional 28 are common between MDD and BPD, and 24 between MDD and SCZ. On the other hand, comparing SCZ and BPD, a greater similarity is observed, with about 146 proteins in common, which supports genomic studies [90–92]. The low overlap among the main psychiatric disorders might support disease specificity at the proteome level.

Additionally, analysis on the STRING—search tool for the retrieval of interacting genes/proteins (http://string-db.org/)—was performed. This platform consists of a database devoted to protein–protein interaction, which provides a

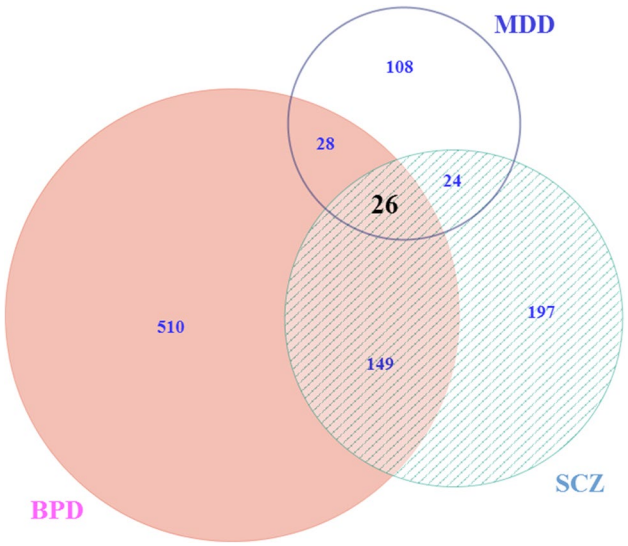

Fig. 1 Venn diagram depicting differences between expressed proteins in schizophrenia (SCZ), bipolar disorder (BPD) and major depressive disorder (MDD)

comprehensive view of the interactions between proteins in the dataset (Jensen, 2008). Therefore, 24 proteins found differentially expressed in all three diseases were analyzed, as observed in Fig. 2. These proteins have a high degree of connectivity between them and are directly related to axonal region of neuronal cells (axon, 0.000334 FDR; neuron projection terminus, 0.000919 FDR; axon terminus, 0.000725 FDR; dendrite, 0.00726 FDR). However, the most correlated cellular component to those proteins was myelin sheath (1.45E−12 FDR), which is formed by oligodendrocytes. These cells are known to be altered in SCZ, MDD and BPD, as shown by both proteomic studies and neuroimaging [94–96], including its maturation process [97, 98].

Myelin is a multilaminar structure surrounding the axons of neurons made by oligodendrocytes in the central nervous system and by Schwann cells in the peripheral nervous system, being an essential structure for the proper functioning of nerve impulse transmission, providing strength and speed [99, 100]. Studies of postmortem tissue in SCZ, MDD and BPD patients showed that myelination-related genes have a reduction in mRNA transcripts in patients [101–103]. Damage to myelin can cause sensory-motor dysfunction, cognitive impairment, mental retardation and even death [100].

The top network found dysregulated, according to IPA (score 28), is related to neurological, psychological and skeletal/muscular disorders, as shown in Fig. 3. This network is composed of 31 molecules, among them 12 proteins are altered in diseases, together with 19 partners of these molecules. This network has a central protein, the TP53, which directly or indirectly connects differentially expressed proteins from all three diseases. This protein has

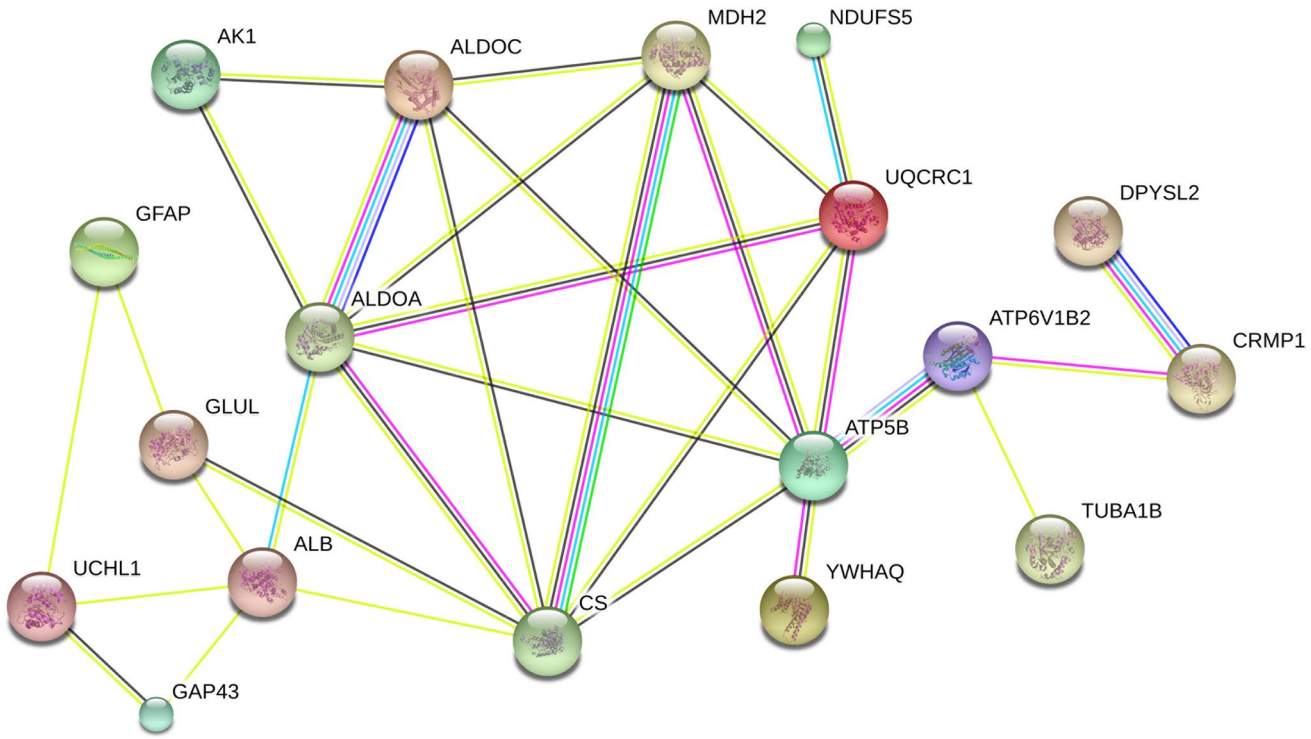

Fig. 2 Differentially expressed proteins commonly found in SCZ, MDD and BPD and their functional correlations using STRING database

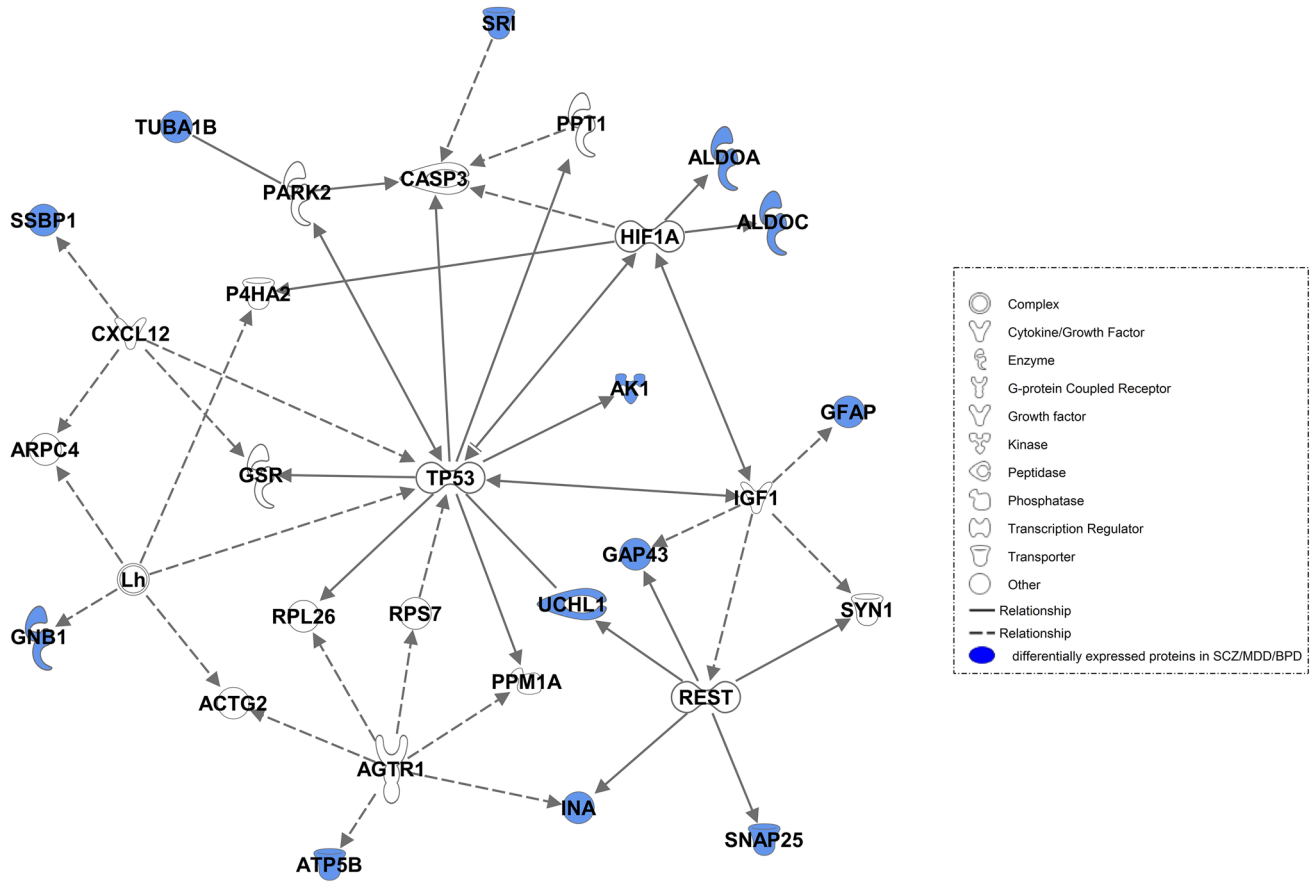

Fig. 3 Differentially expressed proteins and predicted proteins as affected by deregulation them in SCZ, MDD and BPD

anti-proliferation function, plays a role in the maintenance of somatic stem cells [104] and regulates the proliferation and differentiation of neural stem cells (NSC) [105]. Therefore, NSCs maintenance/renewal, migration, differentiation and death can thus be disturbed and have a link with various nervous system disorders, including neurodegeneration and psychiatric disorders [106].

Another molecule, REST (repressor element 1-silencing transcription factor), is also connected to the differentially expressed proteins. This transcription factor is required during differentiation, as induces the expression of neural-specific phenotypes. REST-dependent genes encode transcription factors, transmitter release proteins, voltage-dependent receptor channels and signaling proteins [107]. REST is connected to the differentially expressed synaptosomal-associated protein of 25 kDa (SNAP25), which also plays a critical role in modulating voltage-gated calcium channels and neurotransmitter release [108]. In addition, REST is connected to Alpha-internexin (INA) and GAP43, proteins related to cytoskeleton organization and important function in synapsis and plasticity [109, 110]. These similar connections observed in all three disorders suggest a common synaptic and neurodevelopmental deregulation among them.

Main biochemical pathways of each disorder

In addition to those common features presented, several differentially expressed proteins were only observed in patients with SCZ, which have shown a link with neurological disease (p value 4.18E−03 to 1.09E−40) with 180 proteins involved and psychological disorders (p value 1.29E−03 to 1.09E−40) with 132 proteins. Those observed only in BPD resulted in greater overlap with neurological disease (p value 2.88E−03 to 3.15E−31) with 255 proteins involved and psychological disorders (2.48E−03 to 3.15E−31) with 197 proteins. Similarly, differentially expressed proteins in MDD had 75 proteins involved in neurological disease (p value 2.39E−02 to 3.66E−13) and 55 proteins in psychological disorders (p value 1.92E−02 to 3. 66E−13).

According to IPA, the canonical pathways to which these disorders are associated are energy metabolism pathways deregulation, mainly related to oxidative phosphorylation

mitochondrial dysfunction and gluconeogenesis, followed by cell signaling pathways, including signaling by Rho GTPases family, semaphorin signaling in neurons and 14-3-3 mediated signaling.

Among the leading networks to which SCZ differentially expressed proteins are involved were molecular transport, survival, cell death and neurological disease, with 47 connected proteins. For BPD, the main networks were related to neurological disease, psychological disorders, cellular assembly and organization, with 41 proteins included in those networks. While differentially expressed proteins on MDD were mainly related to cellular assembly and organization, cellular function and maintenance, cardiovascular system development and function, they have shown 37 proteins connected to those networks. As presented in Fig. 4, those proteins have a high connectivity among them, indicating a stronger correlation between pathways, which was recently reinforced by large genome studies with patients of these three disorders [111]. Similarities between those diseases indicate common deregulation basis, yet it is proposed [112] that at some point in development they follow different paths to become distinct disorders.

Schizophrenia

Getting an insight into differentially expressed proteins on schizophrenia brains (21.6 %—25 out of 116 differentially expressed proteins), we observe significant association with 14-3-3-mediated signaling ($p = 1.35\text{E}{-}18$) (Fig. 5). The 14-3-3 proteins are abundantly expressed in the brain and interact with a wide variety of cellular proteins, including kinases, phosphatases and transmembrane receptors [113, 114]. These proteins regulate intracellular signaling, cell division and differentiation, ion channel function, apoptosis, neurodegeneration and dopamine synthesis [114, 115]. Moreover, 14-3-3 proteins have already been implicated in neurological disorders such as Parkinson's, Alzheimer's and Huntington diseases [116], additionally to psychiatric diseases, such as SCZ [117–120].

Indeed, the 14-3-3ζ-deficient mice have significant defects in functions such as working memory, sensory gating and associative learning [121, 122], which are related to long-term synaptic plasticity [122], and defects in neuronal migration [121], integrating symptoms associated with SCZ-like behavior. Antipsychotic medications, such as haloperidol and olanzapine, affect the expression of 14-3-3 proteins [119], endorsing association of this protein family with the disease.

Furthermore, proteins 14-3-3 zeta/delta (YWHAZ) have a broader incidence in the studied brain regions, which was found in five regions (corpus callosum (CC), anterior temporal lobe (ATL), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPC) and mediodorsal thalamus (MDT)). This protein is involved in cell cycle, recognition of DNA alterations, apoptosis, dynamic changes of cytoskeleton and control of gene expression transcription [123]. Furthermore, new evidence indicates an important role in neurogenesis and cell migration [124].

Another protein commonly found altered was glial fibrillary acidic protein (GFAP). The protein was differentially expressed in seven distinct regions [MDT, DLPC, CC, ACC, insular cortex (IC), frontal cortex (FC) and Wernicke's area (WA)]. GFAP is found in glial cells of the central nervous system, being a classical marker for astrocytes [125]. Previous studies showed both GFAP mRNA and protein are decreased in patients with SCZ and BPD [79, 126]. Astrocytes play important roles in brain immune response, synaptic function, debug ions and cellular transmitters, neuronal metabolism and migration [127–129]. Thus, GFAP, as the main protein of intermediate filament in astrocytes, is a widely studied protein in diseases related to brain and is also very important during development [130].

Bipolar disorder

Several diseases, such as SCZ, BPD, Alzheimer's and Parkinson's, have some pathophysiological mechanisms in common, including the production of reactive species of oxygen (ROS) and the accumulation of mitochondrial DNA damage (mtDNA), which together result in mitochondrial dysfunction [131]. Recent studies with BPD patients have revealed differentially expressed proteins and mRNA related to mitochondrial dysfunction [132, 133], particularly oxidative phosphorylation [134]. Mitochondrial dysfunction had higher correlation with BPD, with p value of 9.86E−23 and 24.2 % (40/165), as observed in Fig. 6. In addition, BPD is also associated with mitochondrial DNA (mtDNA) mutations and polymorphisms [135, 136]. These mutations cause an imbalance of mitochondrial enzymes, which can affect energy metabolism. This imbalance can lead to prejudices in major mitochondrial functions, as to synaptogenesis and neuronal plasticity, shown altered in BPD [137, 138].

Furthermore, the proteins superoxide dismutase [Cu–Zn] (SOD1), GFAP and stathmin (STMN1) have been identified differentially expressed in several brain regions of patients with BPD. SOD1 is the major intracellular form of the SOD enzyme family, which catalyze the removal of superoxide free radicals within the cells and are increasingly recognized for their key role in response to oxidative stress [139]. This protein is also associated with replication of stress response genes, DNA damage response, stress response and general Cu/Fe homeostasis [140]. SOD1 is widely associated with psychiatric illnesses on proteomic

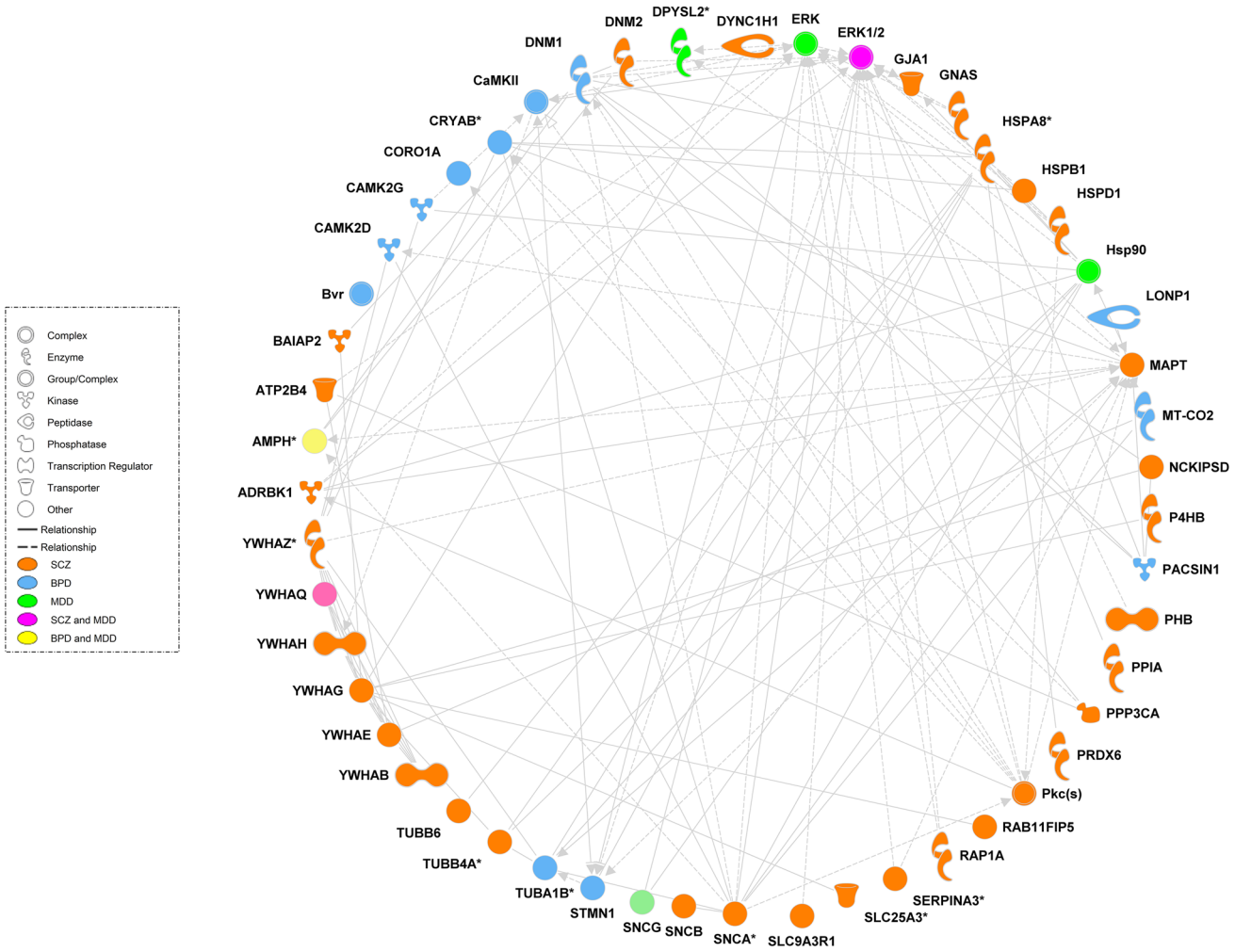

Fig. 4 Interaction network depicting similar proteins among diseases

studies, such as BPD and SCZ, on both blood and brain samples [141–146].

Stathmin, on the other hand, has an important function in mitosis. Moreover, it plays several roles in cellular processes such as the regulation of cell cycle progression, microtubule dynamics, intracellular transport, cell motility, cell polarity and maintenance of cell shape [147]. Stathmin expression has been reported increased during neuronal differentiation, plasticity and regeneration, key functions for proper brain functioning, thus explaining its possible alteration in many neurodegenerative diseases [148].

Major depressive disorder

The leading canonical pathway correlated with MDD was the oxidative phosphorylation (OXPHOS), with *p* value of 3.48E−15, and overlap of 15.4 % of molecules from the pathway (16/104). This pathway, as shown in Fig. 7, is directly related to the mitochondrial dysfunction shown in BPD results. Disorder of the mitochondrial OXPHOS causes biochemical imbalance of the primary route of ATP production, as this pathway is responsible for coordinating the transport of protons and electrons, which leads to energy production [149]. As OXPHOS is a complex pathway, with about 85 proteins, there are a variety of phenotypes related to this route [150]. Disturbances in this pathway frequently occur in psychiatric diseases like SCZ, BPD and MDD [151–154]. Recent studies, using a mutant MDD mouse model, have observed dysregulated OXPHOS pathway gene expression on the hippocampus, which may play an important role in the disease [155].

The main differentially expressed protein in BPD was dihydropyrimidinase-related protein 2 (DPYSL2). This protein participates in regulation of hippocampal neuronal axon formation and establishes neuronal polarization [156, 157]. Recently, the protein interactome of DPYSL2 was

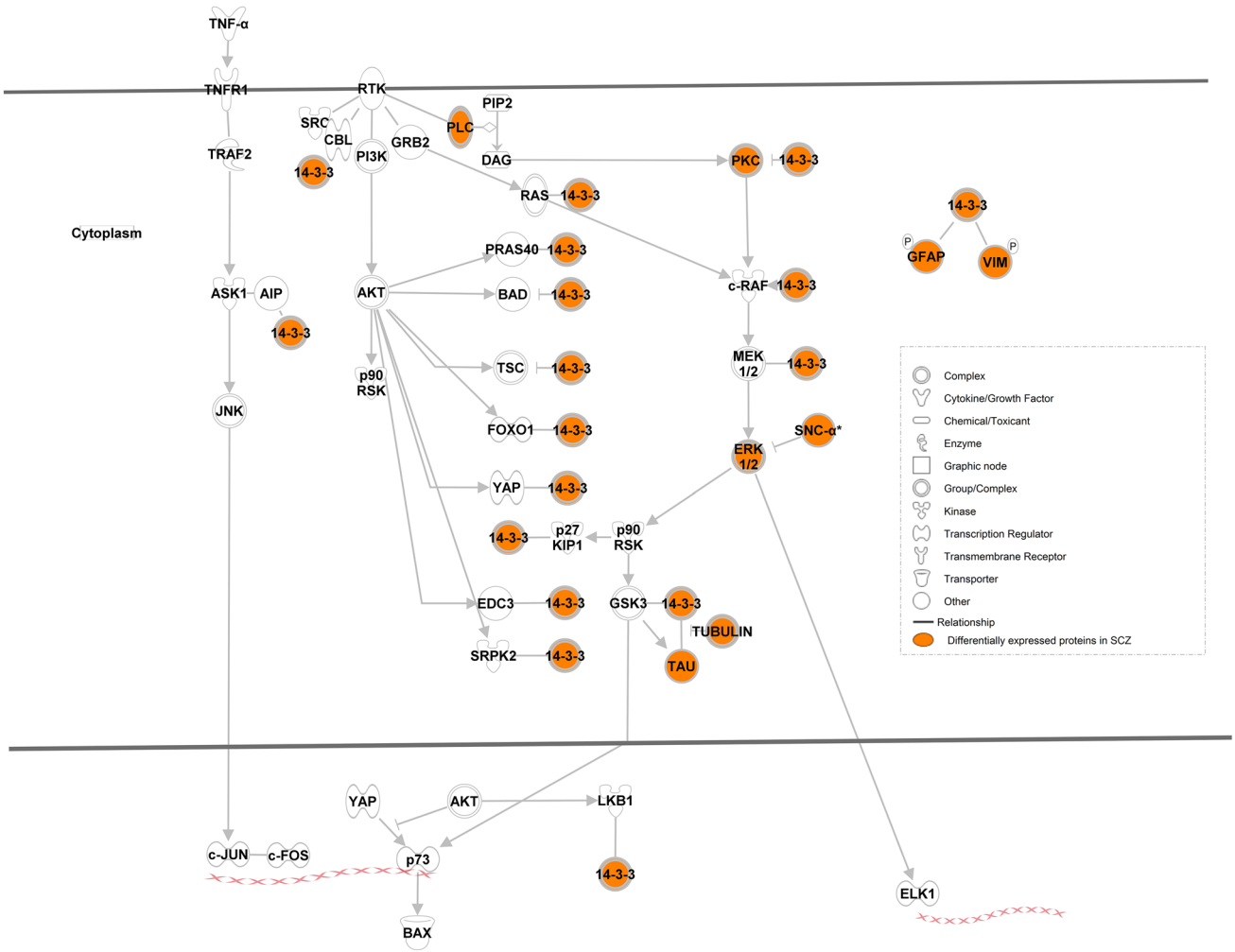

Fig. 5 14-3-3-mediated signaling as the main canonical pathway related to differentially expressed proteins in SCZ

described. Among DPLYSL2 interacting proteins are those involved in axon guidance, along with semaphorin interactions and WNT5A signaling [158]. The protein gene is located on chromosome 8 and is widely associated with neuropsychiatric diseases, such as SCZ, BPD and MDD, and neurodegenerative diseases, such as Parkinson's and Alzheimer [159]. This protein was found at significantly lower levels in the frontal cortex of patients with MDD [79, 87], in addition to the anterior cingulate cortex [69], which may cause abnormalities in neurodevelopment.

Concluding remarks

Mental disorders are common worldwide, affecting 1 out of 5 people [160], and psychiatric disorders contribute significantly to this group. Since they are in general diseases of early ages of onset, these disorders often cause severe damage on patients' lives, such as low level of education, marital instability, occupational status and financial downgrade, as well as high social costs [161–163]. Normally, SCZ, MDD and BPD are only diagnosed when symptoms appear; hence, at this point the disease is already established. As a consequence, disease severity is much higher, proportionally to less effective treatments. Therefore, greater efforts are needed to understand these diseases, aiming for an efficient treatment, thus preventing such damage. Studies in neuroscience have reached enormous progress in understanding the cellular and molecular processes involved in psychiatric diseases [164], but the pathophysiology of these disorders remains undefined [165].

Proteomics holds great promise in the understanding of psychiatric disorders [165], mainly through identification of protein changes in postmortem brains of patients [164], and toward the large-scale analysis of posttranslational modifications [166, 167]. By compiling data from SCZ, MDD and BPD patient research, we have uncovered some similarities referring to signaling pathways altered,

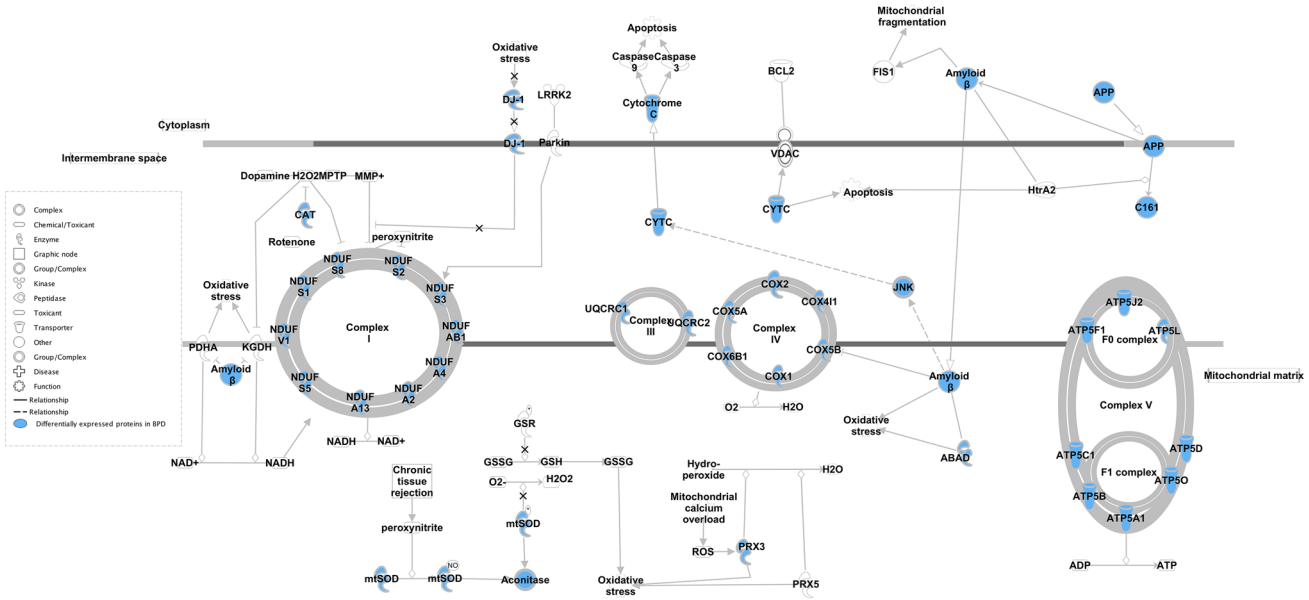

Fig. 6 Mitochondrial dysfunction as the main canonical pathway related to differentially expressed proteins in BPD

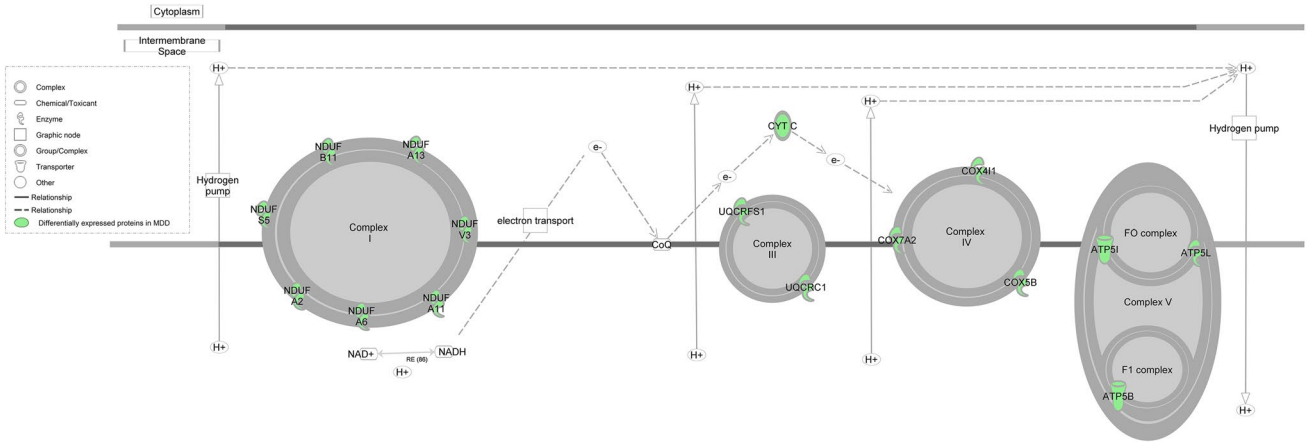

Fig. 7 Oxidative phosphorylation as the main canonical pathways related to differentially expressed proteins in MDD

which are mainly related to energy metabolism and signaling. Nevertheless, each of these diseases has molecular particularities, including most frequent differentially expressed proteins, and deregulation of several canonical pathways, which are unveiled by proteomics. However, currently available data are still inconclusive, and several efforts are in course for better comprehension of biological mechanisms of these diseases. This study also highlights the importance of postmortem brains banks for the better comprehension of psychiatric diseases, particularly regarding proteomic studies, which are used for multifactorial diseases such as psychiatric. In addition, we need more engagement among psychiatrists–researchers: It is possible to improve the access of researchers to these samples, thus increasing the number of researches in this area.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest regarding this subject.

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