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REVIEW

Metabolomics in Schizophrenia and Major Depressive Disorder

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Abstract **Defining pathophenotype, a systems level consequence of a disease genotype, together with environmental and stochastic influences, is an arduous task in psychiatry. It is also an appealing goal, given growing need for appreciation of brain disorders biological complexity, aspiration for diagnostic tests development and ambition to identify novel drug targets. Here, we focus on the Schizophrenia and Major Depressive Disorder and highlight recent advances in metabolomics research. As a systems biology tool, metabolomics holds a promise to take part in elucidating interactions between genes and environment, in complex behavioral traits and psychopathology risk translational research.**

Keywords Schizophrenia, Major Depressive Disorder, omics, metabolomics, systems biology

Introduction

A major component of psychiatric illness risk is polygenic: heritability that arises from many genetic loci having a "small effect." Polygenicity and rare large-effect genetic loci are at the core of complex quest to elucidate under print of psychiatric disorders. Given the limited biological insight obtained through Genome Wide Association Studies (GWAS), the focus of genetic research has shifted to exploring major effect-size contributions (rare copy variants and whole exome sequencing), improving phenotype definition, and attempts to connect various genetic risks to brain mechanisms. In parallel, advances in the bioinformatics, multivariate statistics, and the high-throughput analytical approaches utilized for processing of microarray data have paved the way for further development of the systems biology "panomic" view of the organism, which will be necessary for the successful "unlocking" of psychiatric disorders. However, integration of so called "omics" sciences (genomics, transcriptomics, proteomics, metabolomics) is a formidable task, as it aims to capture the cross-talk between different levels of molecular organization, represented by individual 'omics' sciences. Nevertheless, the implications of such development are very significant, not only for the further advances of our knowledge of molecular mechanisms, but also for psychiatric practice, which lacks specific diagnostic, prognostic, and therapeutic biomarkers in a wide range of diseases.

Metabolites are the final product of interactions between gene expression, protein expression, and the cellular environment. Metabolome presents a state regulated by interactions between genes and environment, and possibly genotype and phenotype. As such, it has the potential to be an informative target for genetic studies of intermediate phenotypes in brain disorders and help illustrate their heterogeneity.

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Schizophrenia

Schizophrenia is a severe complex mental disorder characterized by psychotic symptoms such as hallucinations, delu-

sions, and deficits in executive function (Whitfield-Gabrieli et al., 2009; Milanovic et al., 2011). It affects 0.5%–1% of the world population. Similar to other psychiatric disorders, diagnosis of schizophrenia is based on patient's and family's reports and thus subjective clinical evaluation. The underlying molecular mechanisms of schizophrenia are poorly understood (Yao et al., 2010; He et al., 2012). Symptomatic onset is in early adulthood- factors such as environment, drug abuse, and childhood trauma play important roles, as well as common genetic variations and rare variants. Estimated heritability is 0.80. Although initial genetic studies demonstrated increased risk of *de novo* mutations, larger sample sizes failed to replicate these data. So far, identification of the individual risk genes using Whole Exome Sequencing has had no significant yield. A variation in the Major Histocompatibility Complex locus was shown to have a strong association with schizophrenia at the population level. A follow up study (Sekar et al., 2016) identified complement complex alleles playing the role in synapse elimination during postnatal development. This finding is consistent with reported excessive loss of gray matter and synapses in schizophrenia. In spite of high heritability, clinical heterogeneity remains a major limitation in schizophrenia genetic research. Schizophrenia is not one disease entity, but instead a cluster of clinical symptoms. Identical genomic causation is probably shared only by subsets of schizophrenia patients (Yao et al., 2010; Hosak, 2013). The actual schizophrenia risk will likely be governed by a combination of alleles of small effect size, rare alleles, copy number variations, and epigenetic effects. Complex relationship between genotype and phenotype leading to different clinical presentations in patient sub-cohorts has to be tested, from the genetic variation level to the underlying biologic etiology.

Using downstream products of gene expression, "omics" methods (transcriptomics, proteomics and metabolomics) facilitate the search for plausible disease risk pathways (Allen et al., 2011; Arnold et al., 2015; Botas et al., 2015). A recent metabolomics study (He et al., 2012) demonstrated differences in the amino acid and lipid metabolism in medicated and non-medicated schizophrenia patients when compared to the control group. Subsequent network analysis of these potentially relevant metabolites and known schizophrenia risk genes identified glutamine and arginine signaling pathways as possible risk factors. Another study (Orešič et al., 2011) raised a possibility that there are at least two different schizophrenia related risk pathways, glucoregulatory and proline metabolism.

Amino acids

In addition to glutamine and arginine metabolism, amino acids altered in plasma or cerebrospinal liquid of schizophrenia patients are also involved in nitrogen compound biosynthetic processes. Removal of the α-amino group is the first step in amino acid catabolism, a process essential for the energy production. Removed nitrogen can be excreted as urea or incorporated into other compounds during the anabolic processes. Amonia and asparatate are two sources of urea nitrogen provided by transamination and oxidative deamination.

Arginine is the essential element in the urea cycle. It is produced by various tissues, but hydrolyzed into urea and ornithine exclusively by the liver. Decreased arginine found in schizophrenia could indicate an increase in ammonia and/or nitric oxide (NO) metabolism. Monoamines are one of the sources of ammonia. In the brain, monoamines serve as hormones or neurotransmitters. Altered cerebrospinal fluid monoamine turnover rates and ratios were implicated in genetics of psychosis and schizophrenia (Andreou et al., 2014; Luykx et al., 2014). NO is CNS neurotransmitter. It is also involved in the storage, uptake, and release of other neurotransmitters and oxidative stress. Arginine is one of three substrates for NO synthesis. It is plausible that an increase in arginine consumption may be related to aberrant nitric oxide metabolism in schizophrenia (Yanik et al., 2003; Bernstein et al., 2005; He et al., 2012; Weber et al., 2014)

Data on tryptophan (Trp) metabolites in schizophrenia are inconsistent, possibly due to patient cohort characteristics (first episode vs chronic illness) or the source of biologic sample (blood or cerebrospinal fluid). Trp is metabolized to 5-hydroxytryptamine (5-HT or serotonine) by tryptophan hydrolase (TH) and aromatic amino acid decarboxylase (AAD) in the serotonin pathway. 5-HT is further metabolized to melatonin, which possesses anti-oxidant activity (Reiter et al., 2008). Changes in Trp could reflect a compensatory mechanism due to increased oxidative stress in schizophrenia. Work in the first episode patients (Yao et al., 2010) revealed increased conversion of serotonin to N-acetylserotonin, possibly driving a drop in serum tryptophan levels. Reduction in tryptophan serum availability was also detected in treatment naïve patients (Manowitz et al., 1973; Xuan et al., 2011). In contrast, medicated schizophrenia cohorts demonstrate either increase (Fukushima et al., 2014) or decrease (Manowitz et al., 1973) in Trp and decrease in 5-hydroxyindoleacetic acid (5HIAA) level in plasma (Fukushima et al., 2014) or cerebrospinal fluid (Ashcroft et al., 1966). Earlier investigations suggest that hyperserotonemia may play an etiological role in some forms of schizophrenia (Garelis et al., 1975; Jackman et al., 1983; Stahl et al., 1983). Trp is metabolized to Kyn by tryptophan 2,3-dioxygenase or indoleamine 2,3-dioxygenase in the Kyn pathway (Olney and Farber, 1995; Schwarcz et al., 2001; Fukushima et al., 2014). The kynurenine pathway produces neurotoxic (3-hydroxykynurenine and quinolinic acid) and neuro-inhibitory (kynurenic acid) compounds. At high concentrations, kynurenic acid is a competitive antagonist of the glycine site of *N*-methyl-D-asparate (NMDA) receptors (Stone, 1993) and a noncompetitive antagonist of the α-7-nicotinic acetylcholine receptor at a low concentration (Hilmas et al.,

2001; Alkondon et al., 2004). Thus, increased levels of kynurenic acid may be associated with a spatial working memory dysfunction (Alkondon et al., 2004) though NMDA receptor action. Schwarcz *et al*. (2001) have shown increased cortical levels of kynurenic acid in schizophrenia, which may be related to cognitive impairment. (Yao et al., 2010). Increases in kynurenic acid levels were also reported in the post-mortem brain tissue (Schwarcz et al., 2001) or cerebrospinal fluids (Erhardt et al., 2001) from schizophrenia patients. However, patient's serum kynurenic acid levels remained unaltered, indicating that increased kynurenic acid levels might occur only locally in the brain (Fukushima et al., 2014).

Glutamine is a precursor of γ-GluCys. Lower concentration of glutamine was detected in plasma and elevated glutamate in serum and cortex of patients (He et al., 2012; Fukushima et al., 2014). Interestingly, amonia obtained by removal of alpha amino acid amino group is combined with glutamate to form glutamine, which is transported to the liver to be catabolized to glutamate and ammonia. Additionally, glutamine is an important building block for purine and pirimidine synthesis. The glutamate/glutamine hypothesis of schizophrenia and associated brain metabolic abnormalities in patients and their first degree relatives is well documented (Tandon et al., 2013). A single-nucleotide polymorphism (SNP) in glutamine-dependent carbamoyl-phosphate synthase enzyme involved in glutamine hydrolysis is possibly linked to schizophrenia, (Stone et al., 2007; He et al., 2012; Fukushima et al., 2014). As evidenced by genetic studies, a broader metabolic abnormality might exist in schizophrenia. Comorbid type 2 diabetes mellitus, cardiac autonomic dysregulation, and numerous autoimmune disorders have the strongest familiar predisposition in schizophrenia (Ferentinos and Dikeos, 2012).

Serum glutamate (Glu) is elevated in all psychoses compared to controls. Glutamate is a precursor of ammonia and aspartate nitrogen in the urea cycle. Consequently, glutamate-related metabolic abnormalities may reflect a common, amino-acid pathway abnormality, across different psychoses types (Cherlyn et al., 2010). Serum Glu level is reported to be elevated in treatment resistant schizophrenia, in concert with other amino acid abnormalities, which further supports amino-acid pathway aberrance in schizophrenia (Tortorella et al., 2001).

Upregulation of serum proline was reported in schizophrenia. There is evidence that polymorphisms in the *PRODH* gene encoding proline oxidase are associated with schizophrenia risk (Liu et al., 2002; Kempf et al., 2008) and that the related hyperprolinemia is negatively associated with cognitive performance (Orešič et al., 2011).

Low concentrations of histidine in whole blood and high levels in cerebrospinal fluid were identified in schizophrenic patients (He et al., 2012). Histidine is the histamine precursor. Histamine is an ubiquitous neurotransmitter but also a chemical messenger modulating allergic and inflammatory reactions (He et al., 2012), postulate that downregulation of TCF4, a transcription factor crucially involved in fetal brain development, could probably release its inhibition on histidine decarboxylase, leading to accelerated histidine decarboxylation in schizophrenia (Prell et al., 1995; Fernández-Novoa and Cacabelos, 2001; He et al., 2012).

Ornithine is another amino acid implicated in schizophrenia, due to low plasma levels found in patients. Urea is a major disposal product derived of amino acids amino groups. Ornithine is synthetized in the cytoplasm of liver cells and transported to mitochondria, where it participates in the final stages of urea formation. Increased plasma ornithine implies suppression in the ornithine decarboxylation process (Middleton et al., 2002; He et al., 2012) as a possible aberrant mechanism in schizophrenia patients. Arginine, glutamine, histidine, and ornithine metabolic pathways were associated with schizophrenia genetic susceptibility, based on metabolomic data and schizophrenia risk genes molecular network analyses (He et al., 2012).

Lipids, fatty acids and amino acids associated with phospholipid synthesis

Decreased phosphatidylcholines (PC ae C38:6) in the plasma of schizophrenia patients (He et al., 2012) could imply aberrations in choline metabolism, immune-related signaling, or neurotrophin signaling. Choline is a precursor and metabolite of the neurotransmitter acetylcholine and an essential component of neuronal membrane phospholipids. Phosphatidylcholine serves as substrate for phosphatidylserine synthesis, a major phospholipid located in the inner neuronal membrane. An increase in phospholipase A2 activity in schizophrenia (Gattaz et al., 1987; Gattaz et al., 1990) could implicate acceleration in the breakdown of membrane phospholipids in schizophrenia. Alternatively, an increase in phosphatidylcholine demand would lead to its depletion. The increase in phosphatidylcholine synthesis is a common feature of neuronal differentiation, with nerve growth factor directly modulating this process through immediate early genes and the ERK 1/2 pathway (Paoletti et al., 2011). Outlined findings are consistent with demonstrated cell membrane abnormalities associated with disordered phospholipids composition and metabolism (He et al., 2012).

Saturated triglycerides, small-molecular clusters containing branched chain amino acids, phenylalanine and tyrosine, and proline, glutamic (Fukushima et al., 2014), lactic and pyruvic acids were increased in schizophrenia serum samples, suggesting possible relevance between glucoregulatory pathways, proline metabolism, and schizophrenia (He et al., 2012). A global metabolomic analysis approach coupled with the network analysis identified the lipid cluster LC9, containing saturated and longer chain triglycerides, as the strongest link to schizophrenia (Orešič et al., 2011). In this study, schizophrenia patients were also insulin resistant with

elevated fasting serum insulin levels, which calls for a replication study prodrome or first episode schizophrenia patients. A separate lipidomic study (Kotronen et al., 2009) revealed that the lipids found in LC9 are associated with insulin resistance. Together, these findings imply that schizophrenia, independent of antipsychotic medication and metabolic co-morbidity, is characterized by insulin resistance, enhanced hepatic very low density lipoprotein production, (Kotronen and Yki-Järvinen, 2008) and thus elevated serum concentrations of specific triglycerides (Orešič et al., 2011). Consequently, it is not surprising that fatty acids and ketone bodies were found to be significantly elevated in both the serum and urine sample of the patients, as demonstrated by metabolic profiling (Yang et al., 2013). These metabolic findings could be interpreted as upregulated fatty acid catabolism as a result of insufficient brain of glucose supply (Orešič et al., 2011; He et al., 2012).

Liver mitochondria have a capacity to convert acetyl CoA derived from fatty acid oxygenation into ketone bodies, including 3-hydroxybutyrate. Ketone bodies are used by peripheral tissue as an energy source. Data imply there might be a subset of schizophrenia patients characterized by downregulated fatty acid metabolism, including a decrease in 3-hydroxybutyrate (Yang et al., 2013; Fukushima et al., 2014). 3-hydroxybutyrate also plays a role as the inhibitor of class I histone deacetylases (HDACs). Consequently, a decrease in 3-hydroxybutyrate would downregulate histone acetylation and change DNA transcription, potentially leaving the cell more vulnerable to the oxidative stress (Bitanihirwe and Woo, 2011; Shimazu et al., 2013).

Decreases in linoleic and arachidonic acids (Ramos-Loyo et al., 2013; Fukushima et al., 2014) were identified in some schizophrenia patients. Linoleic acid (LA) is a precursor of ω arachidonic acid (AA) and α linoleic acid, which is metabolized to ω-3 fatty acids, essential in growth and development. Arachidonic acid belongs to long-chain poly-unsaturated fatty acids (LCPUFA), with roles in neuronal development and neurodegeneration. LCPUFA deficiency is associated with schizophrenia and attention deficit hyper-activity disorder (ADHD). In biological fluids, LA and AA are bound to fatty acid binding protein (FABP), which governs the sequesteration of circulating PUFAs. Increase in tissue expression of FABP is closely associated with the etiology of schizophrenia (Maekawa et al., 2011), high-lighting one of the possible biological mechanisms potentially responsible for decrease in LA and AA found in schizophrenia.

Glutathione (GSH) can chemically detoxify hydrogen peroxide (H_2O_2). H_2O_2 is a by-product of anaerobic metabolism, with the potential to cause serious damage to DNA, proteins, or unsaturated lipids which can lead to cell death. Decreases in the GSH level of some schizophrenia patients (Raffa et al., 2009; Fukushima et al., 2014) indicate schizophrenia–consistent with the notion of free radical–mediated neurotoxicity in schizophrenia (Yao et al., 2010). γ-glutamylcysteine (γ-GluCys) is a precursor of an endogenous antioxidant, glutathione (GSH), produced from Glu and Cys by glutamatecysteine ligase (GCL). Interstingly, GCL activity is a rate-limiting enzyme for GSH synthesis, and genetic polymorphisms in GCL significantly modulate schizophrenia risk (Gysin et al., 2007; Nichenametla et al., 2008; Fukushima et al., 2014).

Serine is a substrate for phosphatidylserine synthesis, required for the membrane production. Interestingly, while low levels of serine are found in the peripheral blood of schizophrenia subjects (Hashimoto et al., 2003; Fukushima et al., 2014), the prefrontal cortex is reported to have high level of phosphatidylserine (Wood and Holderman, 2015). Consequently, a dysfunction of oligodendrocyte glycosynapses in the schizophrenia brain could be implicated in peripheral D-serine depletion. D-serine is also a co-agonist of the glycine site of the NMDA receptor. The glutamate hypothesis of schizophrenia etiology suggests that endogenous D-serine is a crucial factor related to the hypofunction of the *N*-methyl-D-aspartate (NMDA) receptor (Schell et al., 1997; Hashimoto et al., 2003). Interestingly, genetic studies identify D-amino acid oxidase (DAO), a molecule highly expressed in the brain where it oxidizes d-serine, as a possible schizophrenia risk (Chumakov et al., 2002; Madeira et al., 2008).

Glucose and lactate

Schizophrenic patients have higher baseline serum levels of glucose and lactate (Xuan et al., 2011). Linkage studies in schizophrenia highlight the possible importance of genes related to glycolysis (Stone et al., 2004). Lactate is a final product of the anaerobic glycolysis in the cells. It signals disordered energy homeostasis: lactate correlates with obesity and type 2 diabetes and modulates diastolic blood pressure. Importantly, stem cell proliferation is ensured through the anabolic state of glycolysis. In contrast, differentiation to adult cells is governed by mitochondrial oxidative metabolism. High levels of lactate decrease neurogenesis in animal models, likely through excessive inflammatory response (Inoue et al., 2015). Similarly, schizophrenia metabolic shift favoring an increase in lactate level could lead to neuronal loss.

Major Depressive Disorder

Major Depressive Disorder is a common psychiatric illness. It is estimated that 10%–15% of people will experience Major Depressive Disorder during their lifetime. Depression is predicted to become the second most common world health problem by 2020. It has relatively low heritability (~0.4) and is clinically heterogeneous. Treatment success is highly variable; less than 50% of patients respond to any given

antidepressant. Such poor response reflects our lack of knowledge of depression biomarkers and their poor clinical characterization. Genetic loci identified by biologic candidate gene studies were not supported by genome-wide studies (GWAS). Failure to identify loci associated with depression from large-scale unbiased GWAS is in part due to a need for a bigger sample size (75 000–100 000) in order to reach comparable power to identify risk loci as has been done in schizophrenia genome-wide studies (Smoller, 2016). Lack of homogeneity in clinical cohorts is an additional significant challenge.

Research on gene-environment interactions (G×E) is growing: there is a strong correlation between stressful life events and depression risk calling for quantification of the stress diathesis model. The allostatic load (AL) is an interdisciplinary approach aimed at quantifying chronic stress in relation to various life pathologies. Allostatic load encompasses the definition of stress as a multidimensional model. Integral parts of this model are genetic and epigenetic factors, early adversities that shape brain development, and hypothalamo-pituitary-adrenal axis responses. These factors include moderation or mediation by environmental toxins, distinctions among socioeconomic status, sex, gonadal hormones and their effects on the brain, and endocrine, metabolic and immune systems. Consistent with AL hypothesis, data indicate that while some Major Depressive Disorder patients have immune related dysfunctions leading to depression, others have energy metabolism impairment, which could be a gate to a disorder (Martins-de-Souza, 2014). Metabolomic analysis findings might improve stratification of heterogeneous Major Depressive Disorder cohorts and facilitate G × E studies. Currently, stratification is based on so called depressive subtypes (by sex, recurrent depression or recurrent vs. early-onset).

Fatty acid and lipid metabolism

β-oxidation is the major fatty acids catabolic pathway, taking place in mitochondia. Carnitine is a molecule essential for the "carnitine shuffle," a process during which a long chain fatty acyl group is transported across the inner mitochondrial membrane. Recent metabolomics analysis (Liu et al., 2015) identified decrease in various plasma acyl carnitine molecules (carnitine C10:1, carnitine C10:2, carnitine C14:2, carnitine C14:3, carnitine C6:0, carnitine C8:0, carnitine C8:1, carnitine C10:0, carnitine C12:1, carnitine C3:0) as possible Major Depressive Disorder biomarker set. Consistent with this finding, there is evidence that Acetyl-l-carnitine may be effective in depression, as adjunct treatment in Major Depressive Disorder or monotherapy in Disthymia (Wang et al., 2014).

Decreased stearic amide and palmitic amide (Liu et al., 2015) levels were reported in plasma of some Major Depressive Disorder patients. Palmitic acid has 16 carbons (16:0) and stearic 18 (18:0). In animal models, palmitic acid induces anxiety like behaviors (Moon et al., 2014). Interestingly, running, which has anxiolytic effect in animal models, decreases palmitic acid concentration in the cortex (Santos-Soto et al., 2013). Palmitic acid was shown to reduces neuronal progenitor cells proliferation (Park et al., 2011) while, stearic acid seems to have neuroprotective effects (Wang et al., 2006).

A variety of lysophospholipids, monoglycerophospholipids, and phosphatidylethanolamines (Liu et al., 2015) were reported as increased in plasma of Major Depressive Disorder patients (16:1 sn-1, LPC 16:1 sn-2, LPE 16:0 sn-1, LPE 16:0 sn-2, LPE 16:1 sn-1, LPE 18:1 sn-2, LPE 22:5 sn-1, LPC 16:0 sn-2d, LPC 18:1 sn-1, LPC 18:1 sn-2, LPC 20:1 sn-2, LPC 22:4 sn-1, LPC 22:4 sn-2, LPC P-16:0, LPE 16:1 sn-2, LPE 20:3 sn-2, LPE 22:5 sn-2, LPE 18:0 sn-1, LPE 18:0 sn-2, LPE 18:2 sn-1, LPE 18:2 sn-2, LPE 20:3 sn-1, PC 32:0, PC 32:1, PC O 36:2, PE 34:2, PE 36:4, PE O 36:6, PE O 34:3, PE O 36:5, PE O 38:7), accompanied with a concomitant decrease in the free fatty acids (FFA 16:2d). Lysophospholipids, monoglycerophospholipids, and phosphatidylethanolamines participate in fuel and energy storage, cell signaling, and ensuring membrane integrity and stability. On the cellular level, the lysophospholipatidic acid receptor modulates survival and apoptosis and serves as a novel cell survival and apoptotic factor (Santin et al., 2009). Antidepressant treatment was shown to increase the release of lysophospholipids in the cortex of mice (Lee et al., 2009).

Decreased plasma levels of lithocholic, deoxycholic, glycodesoxycholic, glycoursodeoxycholic and taurochenodeoxycholic acid (Liu et al., 2015) suggest possible dysregulation of the bile acid metabolism in Major Depressive Disorder. Glycoursodeoxycholic and taurochenodeoxycholic acid were shown to have neuroprotective roles (Vaz et al., 2015; Nunes et al., 2012).

Amino acid and glucose metabolites

Serum glutamate (Glu) and asparate levels are elevated in Major Depressive Disorder compared to controls (Liu et al., 2015). As outlined in Schizophrenia section, glutamate is a precursor of ammonia and aspartate nitrogen in the urea cycle, which occurs exclusively in the liver, and changes in its concentration imply amino-acid pathway abnormality. Serum increases in glutamate and aspartate levels could also reflect a global dysfunction in NMDA receptor function. Ketamine is an NMDA antagonist, blocking glutamate neuronal actions. Rapid antidepressant actions of ketamine underscore clinical applicability of the glutamate Major Depressive Disorder hypothesis for at least a subpopulation of patients.

Higher levels of alanine, taurine, citrate, formate, glycine, isobutyrate, and nicotinate were identified in the urine of

medication naïve, first episode Major Depressive Disorder patients (Zheng et al., 2013). Alanine is a key gluconeogenesis amino acid. High levels of alanine in combination with low brain glucose might imply inefficient gluconeogenesis process. Taurine is a major constituent of bile. In addition to bile acid conjugation, taurine fosters proliferation of human neural stem/progenitor neural cells during fetal brain development (Hernández-Benítez et al., 2013). Citrate could be viewed as a high energy signal. It enables the transfer of acetate units from mitochondria to cytosol, initiating *de novo* fatty acid synthesis. Increases in citrate, in conjunction with high levels of alanine and low glucose, highlights possible gluconeogenesis inefficiency and a shift in the metabolic balance toward fatty acid synthesis. Deceased levels of plasma glucose, lactate, and pyruvate (Zheng et al., 2012) further support putative imbalance between glycolysis and gluconeogenesis energy cycles in Major Depressive Disorder.

In addition to being building blocks for proteins, amino acids are precursors of nitrogen-containing molecules with important biochemical functions: hormones, neurotransmitters, pyrines, and pyrimidines. The serotonergic system is one of the key neurotransmitter systems implicated in Major Depressive Disorder pathophysiology. Seratonin production is highly dependent on plasma tryptophan utilization. A decrease in tryptophan levels directly affects the brain serotonergic system, and metabolomics data reaffirm the tryptophan depletion hypothesis of depression (Moreno et al., 2010; Martins-de-Souza, 2014; Liu et al., 2015). Tyrosine is a building block for cateholamines, dopamine, norepinephrine, and epinephrine. A decrease in tyrosine (Martins-de-Souza, 2014; Liu et al., 2015) could imply increased conversion to cateholamines or deficit in protein catabolism. Cerebrospinal fluid shows reductions in metabolites associated with tryptophan and tyrosine pathways in remitted depression (Kaddurah-Daouk et al., 2012). Tryptophan, tyrosine and methionine pathways might reveal differences between remitted and non-remitted Major Depressive Disorder subjects (Kaddurah-Daouk et al., 2012).

The tricarboxylic acid (TCA) cycle (also known as the Krebs cycle) presents the final pathway for the oxidative catabolism of carbohydrates, amino acids, and fatty acids. Depressed patients' urine (Zheng et al., 2013) was shown to have a decrease in the molecules feeding into the TCA cycle (glucose and piruvate) and an increase in TCA cycle associated metabolites (α-ketoglutarate, succinate, malonate, methylmalonate, and succinyl-CoA). This finding confirms the postulated compromise of glucose metabolism and a shift toward fatty acid and/or amino acid catatabolism with the aim of meeting cell energetic and anabolic needs.

Decreases (Liu et al., 2015) or increases (Woo et al., 2015) in methionine were reported in the plasma of Major Depressive Disorder patients. Methionine derivative is S-adenosyl methionine (SAM), a molecule fundamental to DNA methylation (Cantoni et al., 1989; Kaddurah-Daouk et al., 2012).

Other metabolites and pathways

Serotonin, dopamine, and norepinephrine metabolites (5-hydroxyindoleacetic acid [5-HIAA], and homovanillic acid [HVA]) were decreased in CSF of patients with melancholic depression (Asberg et al., 1984) implying altered serotonine and dopamine brain function, consistent with monoaminergis hypothesis of depression.

Decreased N-methylnicotinamide (NMNA) (Zheng et al., 2013). N-methylnicotinamide is a metabolite of niacin (or nicotinamide) and a decrease in urine concentration could imply niacin deficiency. Biologicaly active coenzyme forms are nicotinamid adenine dinucleotide (NAD^+) and its phosphorylated form, $NADP^+$. Both molecules serve as coenzymes in oxidation-reduction reactions, which could be compromised in depression.

Conclusion

The "Omics" systems biology approach opens a new venue for the quest to identify diagnostic and treatment outcome biomarkers in psychiatry. Unbiased genome-wide studies and pathway analysis hold a promise to identify reproducible disease-risk gene associations. Complex challenges persist, such as disease heterogeneity, polygenicity, and low penetrance of most genetic variants, to name a few. "Omics" tools have a potential to facilitate defining intermediate disease phenotypes (Maletic-Savatic et al., 2008; Vingara et al., 2013; Peterson et al., 2013). Additionally, "*in vivo"* or "*in vitro"* metabolomics may provide valuable insight about G×E interactions.

Recently, genetics studies discovered a possible role of mobile DNA transposomes in the brain cellular heterogeneity (Singer et al., 2010; Evrony et al., 2015). DNA transposomes are transposable autonomous elements, scattered throughout the genome and inherited from one generation to the next. These DNA elements are active and capable of "jumping" during neuronal differentiation, altering individual cell transcriptome and metabolome profiles and thereby modulating functional output through G × E interactions. The human hippocampus has an astonishing 13.7 somatic insertions per neuron (Upton et al., 2015). Bundo *et al*. (2014) found that transposomes may play a role in psychiatric diseases-increases in the copy numbers were evident in cortical neurons of schizophrenia patients and had a positive trend in mood disorders. Moreover, induced pluripitent cell-derived neurons from patients with schizophrenia with 22q11 deletion also had an increase in transposome copy numbers. Human brain somatic transposition was shown to influence the biosynthesis of more than 250 metabolites (Arbusán, 2012), including those linked to schizophrenia.

Hippocampal and/or cortical neuronal mosaicism may be evolutionary imprinted to ensure genomic diversity and greater adaptability to the environment (Glinsky, 2015). It

could also pose a psychiatric risk and contribute to disease heterogeneity. It is in this context that "*in vivo*" (brain) and "*in vitro*" (blood) metabolomics profiling in patient populations could help elucidate G x E interactions and offer an additional tool set for much needed biomarker discovery.

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Compliance with ethics guidelines

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