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A review on diagnostic proteomics of depression

Abstract

Depression is the psychiatric disorder cause when deviation occurs from the standard proteomic condition in individuals. Pathogenesis and etiology of psychiatric disorders are still not clear and many signaling pathways are unknown. In that case the gene provides the primary information about expression of gene and activities of brain. This review focused on the diagnostic proteomics of depression by means of biomarkers. Evidences suggested that reduced and elevated levels of these biomarkers involved in the pathology of depression. These biomarkers could not be used for the diagnostic purposes but also used for the therapeutics. The aim of this non-systematic review article is to evaluate and document a potential importance of proteomics in diagnosis of depression.

Keywords: biomarkers, proteomics, depression, pathology, proteomic, genomic

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Introduction

Depression is a common and severe mental disorder, which can cause a considerable degree of disability to the individual and society.[1] The molecular mechanisms of depression are poorly understood even though many studies have been attempted. Moreover, there are currently no distinctive biological markers to aid in the diagnosis and treatment of depression.[2] The diagnosis, evaluation of medication effects, and prediction of relapse are carried out completely by clinical judgments based on the phenomenology of the disease.[1] The first step requires identifying the molecular pathway for depression. Genomic approaches have attempted to find the underlying molecular pathways, but have not successfully identified the major genes for depression.[3] This may be because there are multiple genes working together or interacting with the environment in a very complex way.[1–3]

Although this genomic information is important, it does not account for the important environmental influences on illness onset, and the presence of a gene does not necessarily reflect functioning protein expression *in vivo*.[4] Many studies indicate that the proteins acts as biomarkers play role in the diagnosis of depression. Serum brain-derived neurotrophic factor (BDNF) would be the most studied protein.[5,6] A recent meta-analyses on 179 association studies concluded that serum BDNF concentrations were lower in untreated depressed patients than healthy control and antidepressant treated patients.[7]. However, one or two protein biomarkers are insufficient to diagnose MDD because proteins usually function in several networks rather than alone. The study of the total set of expressed proteins by a cell, tissue or organism at a given time under a determined condition.[8] Proteomics is basically the study of expression of the protein that is present in any individual that play particular role in the maintenance of the body functions. Proteomics play a vital role in the diagnoses of the alternation in the genetic makeup of the organism that exist in case of the particular disease state.[9] Dynamic proteomic research used fluorescence difference gel electrophoresis, found 42 changed proteins in the liver of chronic restraint stressed rats and validated 3 proteins to suggest how functional proteins act on metabolites to produce energy and process materials. More evidences have shown that stress may have an effect on liver .Proteomic techniques based on Isobaric Tags for Relative and Absolute Quantification [ITRAQ], labeling and liquid chromatography-mass spectrometry [LC-MS] provide a high-throughput approach to analyze differentially expressed proteins in various physiological and pathological states.[9]

Therefore, it is necessary to identify a set of proteins as a biomarker, and proteomics is the most powerful tool to develop a novel biomarker set. Proteomics has diagnostic advantages over genomics because it can reflect post-translational events. The study of total set of proteins expressed by the organism is referred as proteomics which includes gene to gene, gene-environmental interaction and post-translational modifications as well. Proteomics provides the basic information to study the expression of sets of genes that have different influence on the mood variation. In this review, we mentioned some biomarkers that play role in the identification of the depression by analyzing the proteomics in the patients which indicates the variation in the original genetic sequence of the proteins led to the depression.

Biomarkers

Biomarkers are the substances that play role in the identification of the presence and absence of the disease condition, predict treatment responses. These biomarkers act as a marker to mark the alternation in the original sequence of the gene and distinguish the abnormal disease condition from the healthy normal condition. Bio markers are basically the substance that interact the biological system with the hazardous thing which may be chemical, environmental agent and biological substances as well.[10] Here some biomarkers are given below used in depression:

Oligodendrocytes

Oligodendrocytes are the cells present in the brain that play role in the myelination of axons in the central nerveous system. Destruction and alternation in the oligodendrocytes results in the malformation of the myelin sheath that lead to the decrease rate of propagation of the nerve impulse and leakages at the axonal site that particularly destroy the signaling mechanism of the nerve impulse. Dysfuntion of the oligodendrocytes results in the neuronal disorders like schizopherenia etc. Oligodendrocytes are involved in the shortening of the telomere and cause loses of some genes which can be a cause of depression.[11] Mylinated nerve fibers are in case of traumatic brain injury are lost and continue after the post traumatic phase. It cause the damage of oligodendrocytes and the myelinated sheath that is formed by the

oligodendrocytes led to the alternation in the cytoskeleton of the axon results in the depolarization of the central glia cell, ionic disturbance in the axonal region, degeneration of the axon and cause increase in the number of the brain tissues.[12] Glial cell has important role in brain functioning. Glia cells involved in the control of the cerebral functioning and intelligence in the case of depression along with oligodendrocytes, microglia and astrocytes.[13]

Arginine vasopressin

Arginine Vasopressin is a hormone of the posterior pituitary synthesized in the hypothalamus. After synthesis the arginine vasopressin along with its carrier protein (neurophysin) packed into the vesicles and moves towards the axonal ending here they may be release or may be stored. Arginine Vassopressin play role the maintenance of the water level in the body by acting as antidiuretic that increase the permeability of the collecting duct of kidney and also involve in the vasoconstriction of the blood vessels. Arginine Vasopressin involved in the depression. Hyperactivation of the hypothalamic pituatary adrenocortical system cause elevated level of the arginine vasopressin in the blood circulation which indicates the sign of depression.[14] Hypothalamic pituitary adrenocortical is the site of synthesis of the arginine vasopressin and the over expression and hyperactivity of the HPA cause the abnormal increase production of the arginine vasopressin that indicates the phase of depression. The activation of the arginine vasopressin may cause risk factor of depression in rats.[15]

Serotonin

Serotonin is important neuromodulatory due to distinctive neuroplastic capabilities .Synaptic plasticity is a well-known mechanism in learning and memory[16] and dysfunction of synaptic plasticity with neuronal atropy and cell death contribute to pathophysiology of depression.[17,18] 5HT shapes neuronal networks during development and deficiencies there by fundamentally impact the pathophysiology and long term brain disorder.[19] Alteration in serotonergic neuronal function in central nervous system occurs in patients with major depression. There is following reasons in depression patients, (a) reduce CSF concentration of 5-hydroxyindolacetic acid (5HIAA) (b) decrease plasma tryptophan concentration in depression patients (c) reduce concentration of 5 HT and 5HIAA in postmortem of brain tissues of depressed.[20] Tryptophan hydrolase also effect serotonin receptor because alter in TPH2 change the serotonin in depression. 5HTT receptor coded by gene SLC6A4 is altering in depression. 5HTTLPR, Overall distribution of genotype SS/SL/LL were different by risk group. A recessive model best explained the data, with high risk offspring 3-4 times more likely to have both copies of short allele (SS).[21] 5 HTTLPR-rs25531DEFICIwas not significantly association with familial risk. However offspring with two low functional variants had higher rate of MDD. Deficiency of 5HT in depressed patients is due to depletion of tryptophan[22] Tryptophan is an essential amino acid and depletion could affect protein synthesis, less than 1 % of dietary tryptophan is converted to 5-HT.[22] Whereas 95% is metabolized through indoleamine 2,3 dioxygenase pathway giving rise to neuroactive substances quinolinic and kynurenic acid that affect cholinergic /glutaminergic receptor respectively.[23]

SIOOB

It is a biological biomarker and it is used previously for neuropathy and neuroplasticity. It is a neurotropic factor and it is important in neuroplasticity.[24] When a person has depression then this neuroplasticity is disrupted and it is restored by giving antidepressants. We see the SIOOB at serum level by comparing the depressive patients and normal control and also see the difference between those who responds to antidepressants and those who showed no respond. SIOOB level is associated with those who showed response to antidepressants.[25] In depressive patients a high level of serum SIOOB is seen that may increase neuroplasticity. This results in a better response to antidepressant.[26]

Vascular endothelial growth factor (VEGF)

VEGF is a survival and endothelial factor it regulates vascular function. It is present in brain and it has protective effects in neurons.[27] VEGF level decrease by exposure to chronic stress and its hippocampal level increase by giving antidepressants. If VEGF signaling is impaired in brain then it blocks the effect of antidepressants and exercise on hippocampal neurogenesis.[28] Pharmacological antagonism of VEGF-mediated signaling in the brain blocks the behavioral effects of antidepressants in rodent models. Peripheral VEGF play role in neurogenic effects of exercise, which express that in brain VEGF has functional effects. By this we conclude that VEGF is important for behavioral and neurogenic actions of antidepressants.[29] By clinical studies of peripheral VEGF in MDD are mixed. One study reports that MDD patients with peripheral leukocytes in them VEGF expression is increased and when treated with antidepressants then effects are reversed.[30] By comparing another study found no difference in blood VEGF levels between MDD patients and healthy controls that are treated with antidepressants. Further preclinical findings represents that serum VEGF levels are not different in a genetic rat model of depression.[31] These clinical findings are divergent due to important difference in patient community, including gender, age, total counts of depressive an episode that is recurrent vs. acute and comorbid disorders.[32] Depending upon the endophenotype of MDD clinical findings suggest that blood VEGF levels are differentially altered.[33]

C-reactive protein

By the help of meta-analysis it is proved that increase of CRP level occur in major depressions.[34,35] The risk of subsequent depression occurs due to CRP level raising.[35] The CRP level is increased in much condition such as somatic symptoms, atypical depression, old age depression onset, generally depressed man and episodes of cumulative depression and more increasing history of childhood adversity in patients with depression, so for this reason it is used as a biomarker.[36,37] CRP actually cause inflamation, which is more senstively measured by high senstivity CRP. It is most efficient assay than other conventional CRP assays.[38] The new findings about the relationship of hs-CRP and depression are continuing.[39–41]

Cytokines

The most commonly used immune biomarker used in depressed patient is cytokine. In patients of major depression cytokines profiles are usually desturbed. By meta-analysis, increased concentration of tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were identified [41]. IL-1 and IL-6 are also identified in contrast to diagnosis by using standardized inventories,[42] IL-6 level elevations were present in subgroups in depressive disorders which are formally diagnosed.[43] In general community IL-6 level is lower than population taking from in and out door patients. The increased level of soluble interleukin-2- receptor (sIL-2R), TNF-α and IL-6 is present in depressed patients although blood sample compositions influence the effect sizes significantly[44] in serum and plasma sIL-2R and IL-6 were very important while TNF-α were very much different in healthy control by serum measurement, so it is demonstrated through studies

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that there is association between IL-6 and depressive symptoms. It is a pleotropic proinflamatory cytokine whose peripheral concentration was found to be inversely related to hippocampal volume in MDD. The pathogenetic role IL-6 in depression involves the acute phase of response, disorders in zinc and the erythron, HPA-axis activation, induction of the tryptophan catabolite pathway, oxidative stress, autoimmune processes and neuroprogression.[45]

Brain derived neurotrophic factor (BDNF)

BDNF is a protein that codes for a BDNF gene located on the human chromosome 11. BDNF belongs to the neurotrophin family of the growth factor. BDNF play important role in the nourishment, growth and differentiation of neurons. It located at the site of hippocampus, base of forebrain and cortex. It controls long term memory and the learning behavior of the organisms. BDNF involved in the neuronal disorders. Other study on depression suggests that certain alternation in the hippocampal BDNF changes its signaling pathway and cause the depression. The Rg5 stimulates the hippocampal BDNF system.[46] BDNF play vital role in the neurogenesis regulatory mechanism and in the maintenance of the neuronal plasticity. Depression is cause when there is any impairment in the BDNF mechanism.[47] Serum BDNF level is the involved in depression in patient suffering from Systemic Lupus Erythematous (SLE). BDNF level decrease in the patient with SLP disorder that cause depression.[48] BDNF play role in the protection of the neurons and prevent from the changes that cause the alternation in the neural function that led to the suicidal attempt and depression.[49] Depression in case of the diabetes is controlled by the combination of Radix Pueraria and Hawthorn fruit (CRPHF). It reduces the total cholesterol level, random blood glucose and stops the loss of weight in the patients. It prevents diabetes patients from depression.[41] BDNF and proBDNF play role in the production of the neuronal plasticity both of them are opposite in action and mechanism in case of chronic unpredicted mild stress induced depression like behavior. BDFN prevents from the CUMS-induced depression like behavior and pro BDNF cause the CUMS-induced depression like behavior in the hippocampus.[50]

Mechanism of BDNF expression

Tryptophan hydroxylase

Tryptophan Hydroxylase is the rate limiting enzyme of the brain in the synthesis of serotonin. TRH2 gene is located on the chromosome 12q. It play vital role in the usual transmittion of serotonin in the central nervous system. Zhang et al.,[51] identified a 1463G-A transition in TPH2 gene that causes the depression. The TPH2 functional SNP is replace the fix conserved arg441 with the his (R44H) which affect the loss of the serotonin formation when TPH2 was expressed in PCI2 cells. Mutation in the TPH2 cause the defect in the proper synthesis of serotonin that led to the depression.1TPH2 involved in the antidepressant response in the childhood trauma and acts as an antidepressant effect. Alternation in TPH2 plays role the alternation in the serotonin which causes the major depression disorder. Methylation in the promoter region may silence the mRNA expression that causes MDD in patients.[51] TPH2 is the rate limiting enzyme that code for serotonin synthesis and is the risk factor in case of depression. Any mutation and alternation in the TPH2 affect the rate of the serotonin production by decreasing the rate of serotonin formation. Decrease level of the serotonin led to the depression.[52]

VGF derived peptides

VGF is a neuropeptide. Its Precursor polypeptide in the presence of neuroendocrine-specific pro-hormone convertase PC1/3 and PC2 produce mature peptides (VGF) which are routed in endoplasmic reticulum and in depression it is released.[53] VGF consist of larger and smaller C terminal fragment (NAPP-129) and (TLQP-62).[54] VGF is present on 7q22 chromosome in humans while on 5th chromsome in mice.[55] VGF is expressed in neurons and present in many brain parts.[56] Excision of VGF gene shows that deficiency of energy balance and regulation of homeostasis occur as well as hyperactivity hypermetabolism and infertility occur.[55] VGF derived peptide act as an antidepressant.[53] VGF cause long term and persistant changes in behavior of depressed patients.[54] VGF is essential regulator of mood. The decreases in level of VGF occur in CSF of patients with neurodegenrative disease.[57] Induction of VGF occurs by BDNF, 5HT, antidepressant drugs and exercise.[55] The downregulation of neuropeptide occurs in depressed animal models such as learned helplessness and force swim test. Synaptic charge is increase in hippocampal cultures by VGF and enhancement of neurogensis *in vivo* study of dentate gyrus. Recently, VGF (TLQP-62) has also been shown to potentiate synaptic transmission in hippocampal slices via TrkB-dependent mechanisms suggesting an interaction between VGF and BDNF in the modulation of hippocampal synaptic function[58–60] and VGF derived peptides are used as biomarker of depression.

Conclusion

The present study demonstrates that the biomarkers are associated with the depression. There are several biomarkers those varying levels indicates the depression. Deviation from the normal level of the biomarker in healthy person may lead to the symptoms of the depression in the patients. Proteomics is the only study that is widely involved in depression because the change in the protein sequence may lead to the depression. To study the different levels of biomarker involved in the depression many techniques are used that play role in providing the detailed proteomics of the depression. By studying the body fluid of depressed patients we identified markers which led to suicidal attempt and perform brain function. Depression is basically a neuronal disorder so there is no permanent cure of depression. Antidepressants are used to treat the depression not to completely get rid of depression but only for temporary treatment.

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Conflict of interest

The author declares no conflict of interest.

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