

Roles of PTEN/PI3K/AKT/GSK3 β Pathway in Neuron Signaling Involved in Autism

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Abstract

Autism spectrum disorder is a set of neurodevelopmental disorders in terms of prevalence, morbidity and impact to the society, which is characterized by intricate behavioral phenotype and deficits in both social and cognitive functions. The molecular pathogenesis of autism spectrum disorder has not been well understood, however, it seems that PI3K, AKT, and its downstream molecules have crucial roles in the molecular pathogenesis of autism spectrum disorder. The PI3K/AKT signaling pathway plays an important role in the regulation of cell proliferation, differentiation, motility, and protein synthesis. Deregulated PI3K/AKT signaling has also been shown to be associated with the autism spectrum disorder. Discovery of molecular biochemical phenotypes would represent a breakthrough in autism research. This study has provided new insight on the mechanism of the disorder and would open up future opportunity for contributions to understand the pathophysiology.

Keywords: Autism; ASD; PI3K; AKT; PTEN; GSK3; Signal transduction

Abbreviations:

ASD: Autism Spectrum Disorder; DHA: Docosahexaenoic Acids; EPA: Eicosapentaenoic Acid; GSK3: Glycogen Synthase Kinase 3; 5-HT: 5-Hydroxytryptamine, Serotonin; mTOR: Mammalian Target of Rapamycin; NF- κ B: Nuclear Factor κ B; PDZ: PSD-95/Dlg/ZO-1; PH: Plekstrin Homology; PIP3: Phosphatidylinositol (3,4,5)-Triphosphate; PI3K: Phosphatidylinositol-3 Kinase; PPAR γ : Peroxisome Proliferator-Activated Receptor γ ; PTEN: Phosphatase and Tensin Homolog on Chromosome 10; PUFAs: Polyunsaturated Fatty Acids; ROS: Reactive Oxygen Species; SSRIs: Selective Serotonin Reuptake Inhibitors; TNF: Tumor Necrosis Factor; TSC1: Tuberous Sclerosis Complex 1; TSC2: Tuberous Sclerosis Complex 2

Introduction

Autism Spectrum Disorder (ASD) is a group of neurodevelopmental disorders defined by an abnormal functioning with the fundamental deficits in social communication and reciprocity, and shows repetitive and categorized patterns of behavior [1,2]. ASD is one of the most common behavioral disabilities diagnosed in children, which represent a major public health problem. ASD continues to increase at an upsetting rate [3]. Mixtures of genetic as well as environmental factors are thought to cause the ASD, and more active treatments than those now presented are absolutely required. Several genetic studies have identified a large number of genes which are related to ASD [4]. Many of the genes implicated in ASD encode synaptic proteins [5]. However, most of those gene mutations are rare and may only account for a small part of the cases of ASD. Neuropathological methods applied to ASD brains have revealed several developmental macroscopic and microscopic abnormalities [6], suggesting neuro-inflammation with cytokine

production in frontal cortex and cerebellar regions have occurred [6]. In addition, intracellular signal transduction systems including the phosphoinositide 3-kinase/serine-threonine protein kinase AKT (also known as protein kinase B)/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway in brain have been found to be altered in the ASD patients [7]. Furthermore, gene mutations associated with the regulation of this pathway seem to play a significant role in mediating the behavioral abnormalities characterized in the ASD. Because the pathway also seems to make immune cell activation by regulation of the key inflammatory cytokines [8], changes in the inflammatory signaling might contribute to specific therapeutic effects on ASD treatment. Moreover, recent studies have indicated that several abnormalities of serotonergic system have been described in patients with ASD including abnormal activity of the transporter and reduced serotonin synthesis in brain [9]. Serotonin exerts part of its action by modulating the activity of PI3K/AKT [10,11]. Here, we provide an overview of research on the characterization of the regulation of PI3K/AKT signaling (Figure 1) at the viewpoint of pathogenesis in ASD. Understanding those regulations may provide better efficacy of new therapeutic approaches.

Relationship between ASD and Serotonin/GSK3 β signaling

Serotonin (5-HT) is involved in various aspects of normal brain functions including the regulation of mood, appetite and social interactions [12,13]. Accordingly, a neuro-contribution of 5-HT transmission in various human psychiatric conditions and drugs acting on the 5-HT neurotransmission are regularly used for the management of anxiety disorders [14]. Dysregulation of brain 5-HT neurotransmission is thought to surely underlie mental conditions in ASD [9]. Studies have found raised 5-HT levels in the whole blood cells and platelets of ASD patients [15,16]. Higher activity of 5-HT transporter has also been implicated in ASD [17]. 5-HT itself or drugs

acting on the 5-HT neurotransmission control the serine/threonine kinase glycogen synthase kinase 3beta (GSK3 β), a signaling molecule modulated by a lot of psychiatric therapeutic agents [1,18]. For example, aripiprazole is an atypical antipsychotic drug accepted for the treatment of psychiatric disorders such as schizophrenia, bipolar disorder, major depressive disorder, and ASD [19]. The drug shows partial agonistic activity at the 5-HT(1A) receptors, and antagonistic activity at the 5-HT(2A) receptors [20]. Furthermore, GSK3 β inhibition rescues behavioral abnormalities in the 5-HT-deficient mice [21]. In addition, reduction in brain 5-HT levels is accompanied by activation of the GSK3 β [13]. Considerably, inactivation of GSK3 β using pharmacological or genetic methods, may improve the aberrant behaviors formed by the 5-HT deficiency. Furthermore, multiple classes of 5-HT drugs, including selective 5-HT reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors, and atypical antipsychotics, inhibit brain GSK3 β signaling [22-24]. GSK3 β is inhibited by lithium, which is often used in combination with antidepressants for the management of certain mood disorders [25].

of inhibiting GSK3 β activity by increasing the inhibitory phosphorylation of the amino-terminal domain serine-9 residue [33,34]. Although the GSK3 β was first identified as an enzyme phosphorylating glycogen synthase, it has been found to phosphorylate a lot of intracellular substrates [35]. Through the phosphorylation, GSK3 β regulates many important cellular processes, including development, cell structure, microtubule dynamics, gene expression, and cell survival [35]. GSK3 β is a ubiquitous serine/threonine kinase which is usually referred to as GSK3 isoforms, GSK3 α and GSK3 β [36]. These two iso-enzymes are the product of different genes termed GSK3 α and GSK3 β . The development of GSK3 isoform-specific inhibitors seems to be necessary for the treatment with the GSK3-mediated pathology [37]. The regulation of GSK3 by 5HT(1A) receptors appears to involve an activation of phosphoinositide 3-kinase (PI3K) which in turn activates the serine/threonine kinase AKT, then phosphorylates the inhibitory serine 9 residue of GSK3 β [27]. In addition to its regulation by 5-HT, brain GSK3 β is also inactivated by several neurotrophic factors, such as the brain-derived neurotrophic factor and its receptor TrkB through PI3K-mediated signaling [38,39]. Drugs that influence the 5-HT system can also regulate GSK3 β in certain brain areas [21]. Accordingly, systemic inhibition of GSK3 β has been shown to have effects similar to those of mood stabilizers, antipsychotics or antidepressants. Numerous classes of pharmacological compounds may differentially modulate GSK3 β activity in the brain neuronal networks.

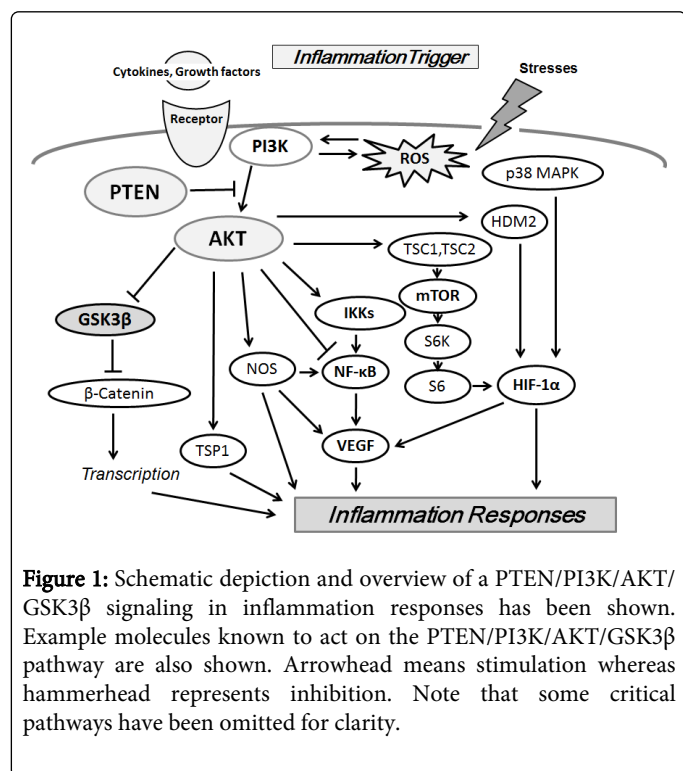


Figure 1: Schematic depiction and overview of a PTEN/PI3K/AKT/GSK3 β signaling in inflammation responses has been shown. Example molecules known to act on the PTEN/PI3K/AKT/GSK3 β pathway are also shown. Arrowhead means stimulation whereas hammerhead represents inhibition. Note that some critical pathways have been omitted for clarity.

Unlike many kinases, the GSK3 β is a constitutively partial active kinase that is inhibited following the phosphorylation of the Ser-9 residue located in its amino-terminal domain [26] (Figure 2). In brain, stimulation of 5-HT (1A) receptors augments phosphorylation of the Ser-9 residue, thus leading to inhibition of the GSK3 β [27]. In contrast, 5-HT (2A) receptor signaling reduces GSK3 β phosphorylation thus leading to kinase activation [28]. Inhibition of this kinase prevents the appearance of behavioral changes brought by 5-HT-deficiency in mice experiments [29]. Accordingly, targeting GSK3 β signaling may give therapeutic advantages for the controlling of certain 5-HT-related psychiatric conditions. In consistent, inhibitory serine-9 phosphorylation of GSK3 β is also essential for the action of lithium [30]. Either directly or indirectly, mood stabilizers lithium and valproic acid trigger an inhibition of GSK3 β [31,32]. In addition, various drugs acting on 5-HT neurotransmission are capable

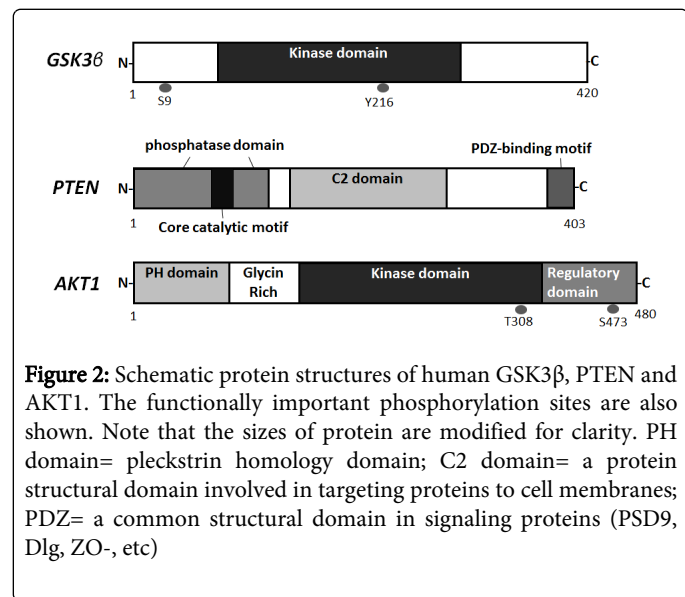


Figure 2: Schematic protein structures of human GSK3 β , PTEN and AKT1. The functionally important phosphorylation sites are also shown. Note that the sizes of protein are modified for clarity. PH domain= pleckstrin homology domain; C2 domain= a protein structural domain involved in targeting proteins to cell membranes; PDZ= a common structural domain in signaling proteins (PSD9, Dlg, ZO-, etc)

Relationship between ASD and PTEN

Increasing form of evidence suggests dysregulated PI3K activity and downstream signaling as a significant contributor and potential therapeutic targets for mental disorders [7,40]. Signaling through the PI3K has various essential roles such as cell growth, migration, differentiation and cell survival [41]. The PI3K activity is also known as a crucial regulator of neuronal function [42]. PI3K signaling transduces various signals from cell surface receptors to the AKT/mTOR pathway, and is crucial for synapse and dendritic spine development [42], and for enduring forms of synaptic plasticity underlying memory and learning [43]. Accordingly, alteration in the PI3K/AKT/mTOR pathway results in many behavioral abnormalities

and is also expected to play a significant role in ASD pathogenesis. Actually, alteration of the downstream mTOR signaling pathway has been shown to be involved in 14% of ASD individuals [44]. Phosphatase and tensin homolog on chromosome 10 (PTEN) has lipid phosphatase activity against the 3'phosphate of phosphatidylinositol γ 5 trisphosphate, which negatively regulates the activity of PI3K/AKT pathway [45]. In other words, PI3K catalyzes the reverse of PTEN reaction resulting in AKT activation. Then, AKT phosphorylates a diverse set of substrates including GSK3 β [46]. 5-HT promotes interactions with a scaffolding and regulatory molecule, which results in the activation of PI3K/AKT [47]. Therefore, the PTEN may be a significant regulator of this pathway in mediating the ASD phenotype. In a clinical cohort of pediatric patients with ASD, there is a prevalence rate of about 8% with mutations in PTEN gene [48]. Developmental delay and/or mental retardation have a higher prevalence rate with mutations in PTEN [49]. Functional absence of PTEN results in an enlarged hippocampus with increased size of brain dendrite [50]. In contrast, overexpression of PTEN has been shown to have inhibitory effects on 5-HT signaling via the decreased AKT activity [51]. It has been shown that PTEN is a tumor suppressor gene mutated in a lot of human cancers [52]. Individuals with germline PTEN mutations are susceptible to tumors but also display brain disorders together with macrocephaly, seizure, and mental retardation [53]. As mentioned above, PTEN mutations have also been reported in ASD individuals [54]. Downstream of the PI3K/AKT pathway, some components of the mTOR signaling are present in synapses and mediate synaptic plasticity in specific neuronal residents [55]. So, abnormal activation of the PI3K/AKT pathway could underlie behavioral abnormalities reminiscent certain features of human ASD. However, a causal link between PTEN and ASD remains unclear.

Diets may contribute to the improvement of ASD-therapy via the modulation of PTEN/AKT and GSK3 β signaling

Fish oil administration amends cognitive deficit, increases AKT phosphorylation, decreases GSK3 β phosphorylation, and decreases pro-apoptotic molecule-expression, suggesting a potential role for fish oil as a protection of neurons [56]. In particular, omega-3 (n-3) long-chain polyunsaturated fatty acids (PUFAs) in the fish oil have become a focus of interest. Docosahexaenoic acids (DHA) are essential for brain development [57]. Fish oil administration also improves cognitive deficit by the increasing AKT phosphorylation [58]. Accordingly, neuroprotection could be performed by certain diets involved in PI3K/AKT pathway. A variety of signals from food nutrients leads to the PI3K/AKT and GSK3 β pathway activation and/or inhibition (Figure 3). For example, phosphorylation of Ser9 in GSK3 β is significantly increased in green tea polyphenols-treated HepG2 cells [59]. In mice experiments, resveratrol may provide neuroprotection via the increases in the GSK3 β phosphorylation [60]. Dietary depletion of tryptophan, which is the precursor of 5-HT, has been shown to exacerbate the repetitive behavior in ASD patients [61]. In consistent, tryptophan-restricted animals display a reduced activity of phosphorylated AKT [62]. It is also suggested that the neuroprotection of curcumin might be mediated via PI3K/AKT signaling pathway [63]. Curcumin, a component in the widely used culinary spice turmeric, could improve the plasticity and structure of synapse, and could improve memory capacities [64]. Furthermore, an apparent anxiolytic effect of curcumin has been shown in lead induced animal anxiety-model, possibly resulted from modulation of neuronal 5-HT neurotransmission [65]. Kaempferol is a flavonol present in

various plants such as grapefruit and some edible berries, which induces the activation of PI3K/AKT signaling [66]. On the contrary, the biological activity of the isothiocyanates, rich in some vegetables such as broccoli, has been shown to suppress AKT phosphorylation [67]. However, despite these experimental observations, the exact mechanisms for these food ingredients remain elusive for the clinical uses. Additionally, it seems essential to exploit the potential profits of optimal treatment and/or combination with these PI3K/AKT modulators.

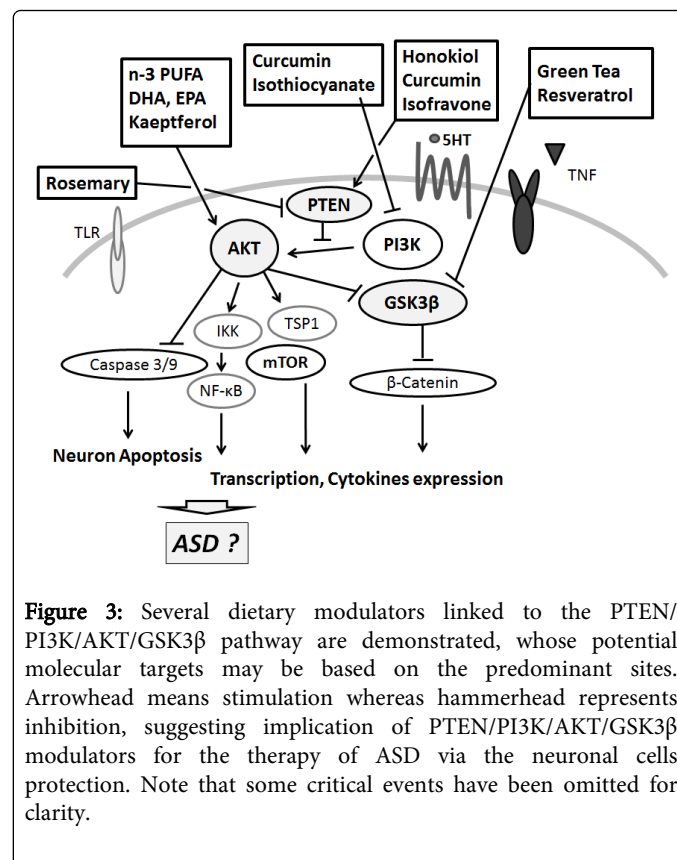


Figure 3: Several dietary modulators linked to the PTEN/PI3K/AKT/GSK3 β pathway are demonstrated, whose potential molecular targets may be based on the predominant sites. Arrowhead means stimulation whereas hammerhead represents inhibition, suggesting implication of PTEN/PI3K/AKT/GSK3 β modulators for the therapy of ASD via the neuronal cells protection. Note that some critical events have been omitted for clarity.

Therapeutic and/or dietary interventions to respond the reduction of PTEN expression could contribute to the prevention of the anxiety diseases and/or could decline the rate of its development. Honokiol, a compound in traditional eastern herbal medicines, can chemically diminish the PI3K/AKT signaling by up-regulation of PTEN expression [68]. However, PTEN indirectly promotes 5-HT synthesis and secretion via inhibiting the signaling [69,70]. In addition, there is a crosstalk between PTEN and 5-HT receptor [70]. It has been shown that DHA and eicosapentaenoic acid (EPA) increase the level of PTEN in breast cancer cells [71]. Since DHA and EPA are ligands of PPAR γ , both of the n-3 PUFAs exert anti-proliferative effects by inducing PTEN expression via the activation of the PPAR γ [72]. In this meaning, the most attractive target with regard to PTEN transcription seems to be PPAR γ [73]. Both genistein and quercetin, daidzein also have an effect on the PPAR γ activation which has been shown to up-regulate PTEN expression, then, suppresses the PI3K/AKT pathway [74]. Therefore, dietary exposure to the soy isoflavones at physiologically relevant concentrations induces PTEN expression [75]. A high-fat diet raises circulating fatty acids, which considerably modifies PTEN expression [76]. Remarkably, some of rosemary extract represses PTEN expression in K562 culture cells [77].

Additionally, dietary consumption of the indole-3-carbinol up-regulates PTEN in the animal model [78]. In the future, these findings might be interpreted into new dietary managements for the treatment of ASD via the regulation of AKT/PTEN signaling pathway.

Perspective

Overall, the effect of depletion in brain GSK3 β activity is a reduction in anxiety that is combined with an increase in the beginning of social interaction. As mentioned above, previous studies have shown that GSK3 β would be commonly activated by 5-HT (2A) receptors and inhibited by 5-HT (1A) receptors [27,28]. Changes in the regulation of GSK3 β activity have been associated with the actions of several psychoactive drugs, including those affecting 5-HT functions in the treatment of mood disorders. A better understanding of the functions of GSK3 β in different brain areas may be the key to unravel the mechanisms by which it contributes to the regulation of ASD treatment. Investigations of the function and mechanisms of GSK3 β mediated signaling in 5-HT synaptic transmission should offer research possibilities to understand and potentially manage human disorders. PTEN/PI3K/AKT/GSK3 β pathway seems to be critical for maintenance in brain neurons. As enzymes involved in neuronal cell survival and neuroplasticity is particularly relevant to the function of neurotrophic factor, regulation of PTEN/PI3K/AKT/GSK3 β may provide an important signaling for the neuroprotection in ASD. Among different signaling molecules that can be regulated by 5-HT, several lines of evidence support a role for this signaling networks underlying the development and treatment of mental illnesses. Accordingly, one treatment model is based on the regulation in the ASD children. Given the complexity of the signaling pathways that can regulate brain activity, it is probable that this pathway might contribute to the therapeutic effect of dietary treatment on ASD. The benefits from dietary supplementation may extend to a wider population.

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