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·Review·

Role of the PTEN signaling pathway in autism spectrum disorder

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Autism is an etiologically heterogeneous group of neurodevelopmental disorders, diagnosed mostly by the clinical behavioral phenotypes. The concept that the tumor-related gene *PTEN* plays a critical role in autism spectrum disorder has emerged over the last decade. In this review, we focus on the essential role of the *PTEN* signaling pathway in neuronal differentiation and the formation of neural circuitry, as well as genetic mouse models with *Pten* manipulations. Particularly, accumulated data suggest that the effect of PTEN on neural stem-cell development contributes significantly to the pathophysiology of autism spectrum disorders.

Keywords: *PTEN*; *TSC1/2*; autism; synapse; neural stem cells

Introduction

The phosphatase and tensin homolog (*PTEN*) gene on chromosome 10 was initially identified as a tumor-suppressor gene that is frequently mutated in human cancers. Further studies showed that PTEN plays an important role in brain development[1, 2]. Human genetic studies showed that *PTEN* germline mutations result in macrocephaly, seizures, and mental retardation[2-4]. Biochemical studies showed that PTEN negatively regulates the phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway[1] (Fig. 1A). Its lipid phosphatase function directly counteracts PI3K activity, thereby inhibiting the activation of AKT. The PI3K/AKT pathway is indispensable for regulating cell growth, survival, and proliferation. Therefore, abnormalities in the PI3K/AKT/mTOR pathway lead to neurological and psychiatric disorders such as brain tumors, autism, and schizophrenia.

A component of the PI3K/AKT pathway, tuberous sclerosis complex 1/2 (TSC1/2) was initially identified as a tumor-suppressor, but further studies found that it is essential for normal brain development and function. TSC1 interacts with TSC2 to form a dimer that has physiological functions. TSC1/TSC2 inhibit mammalian target of rapamycin complex 1 (mTORC1), which is a regulatory factor for mitotic cell growth, and this suppression is released by AKT-mediated TSC2 dephosphorylation[5-7] (Fig. 1A).

Autism spectrum disorders (ASDs) include a variety of neurodevelopmental symptoms[8]. They affect ~7 per 1 000 children and are marked by impaired social relationships, communication deficits, and stereotyped and repetitive behaviors. Seventy percent of ASD cases are associated with mental retardation[9-11]. Still, the genetic basis of ASDs remains largely unknown. So far, hundreds of genes and many chromosome regions have been proposed to be associated with ASDs. In this review, we summarize the recent genetic and neurobiological findings and hypothesize that the PTEN signaling pathway plays a critical role in the pathophysiology of ASD, ranging from multiple aspects of neural development such as neurogenesis, synapse-formation and plasticity, to the structural and functional plasticity of neural circuitry (Table 1). We also discuss available mouse models with genetic manipulations involving the PTEN signaling pathway.

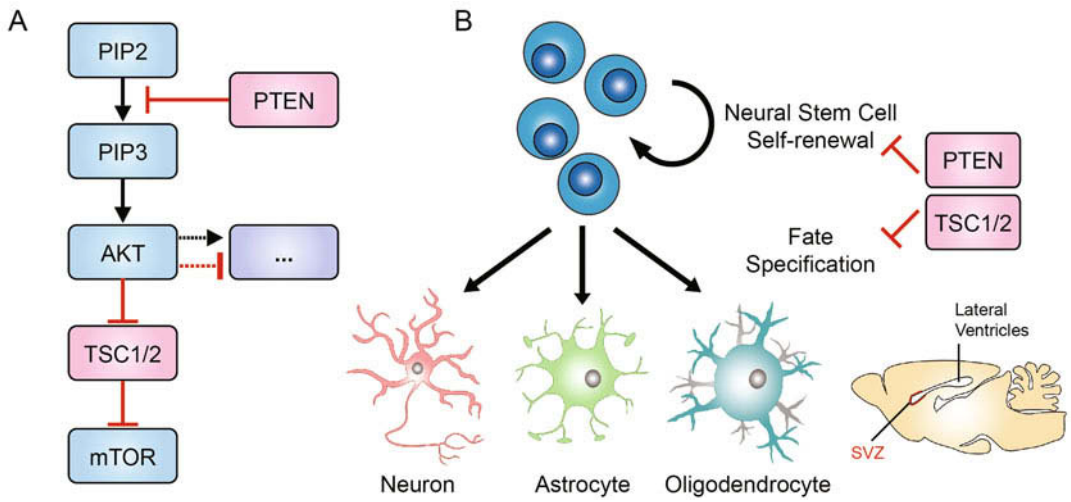

Fig. 1. PTEN-TSC1/2-mTOR in neural stem cell (NSC) regulation. A: PTEN is a negative regulator of the AKT pathway. In the AKT pathway, TSC1/2, an mTOR activator, is inhibited by AKT. B: NSCs are self-renewing and multipotent cells. They differentiate into neurons, astrocytes, and oligodendrocytes with distinct stimuli. NSC properties are upregulated with PTEN or TSC1/2 disruption.

Table 1. Recent findings of the PTEN signaling pathway in autism spectrum disorders

	PTEN	*TSC1/2*
Disorder	ASD with macrocephaly[12]	Tuberous sclerosis complex[13-15]
Rate of autism	1–17%[16]	~25–60%[13-15]
Rate in autism	1%[16]	1.1–1.3%[17-19]
Synapse development	Overgrowth[20, 21]	Hypertrophy[22]
Animal models	Macrocephaly, social behavior deficits, seizures, anxiety, learning deficits[20]	Macrocephaly, seizures, learning and memory deficits, anxiety [23, 24]

Genetic Mutations of the PTEN Signaling Pathway in ASD Patients

Studies of *PTEN* mutation frequency in ASD patients show discrepancies across different studies most likely due to genetic variations among populations. Geneticists have screened the *PTEN* mutations in children diagnosed with autism and macrocephaly independently, and reported that their frequency is ~1%[16], 8.3%[25] and 17%[12]. The head circumference of the included children and whether they were from simplex or multiplex families may explain the inconsistencies among studies. Autism with extreme or familial macrocephaly may have a much higher *PTEN* mutant rate[12]. When Buxbaum *et al.* undertook *PTEN* gene mutation analysis in patients with ASDs and macrocephaly, they showed ~1% *PTEN* mutations in all participants with macrocephaly from multiplex families, who were the only macrocephalic individuals in the family[16]. In the future, more comprehensive analysis of the *PTEN* gene in a greater number of patients with autism would give a more complete picture of the prevalence of *PTEN* mutations in autistic people. Moreover we still need to consider the possibilities that a reduction in PTEN level may occur either by genetic mutation or by epigenetic mechanisms within specific brain regions, which would not be detectable in peripheral blood samples[26].

Either *TSC1* or *TSC2* gene mutation causes human tuberous sclerosis complex (TSC) and 25–50% of these

patients exhibit phenotypes related to ASD[13-15]. In patients diagnosed with ASD, 1.1–1.3% have TSC[17-19]. Children with TSC and *TSC2* mutations are more likely to develop autism than those carrying *TSC1* mutations. Children with *TSC2* mutations are more likely to be diagnosed with autism if they show early-onset infantile spasms and temporal lobe tubers screened by MRI[27]. In one study, Jeste *et al.* showed that ~50% of children with TSC have autistic phenotypes, based on the Autism Diagnostic Observation Schedule (more specifically 66% at 1.5 years of age, 54% at 2 years, 46% at 3 years, and 50% at 5 years)[28]. Furthermore, the cognitive functions of children with TSC and ASD phenotypes are more severely impaired than those without autism[28].

Role of the PTEN Pathway in Neuronal Fate Determination and Differentiation

Brain-specific *Pten*-deficient mice provide a good model to investigate the role of PTEN in the proliferation and differentiation of neural stem/progenitor cells (NSCs)[29, 30]. The mouse brain becomes abnormally large when *Pten* is deleted from embryonic NSCs. Further analysis showed that this results from increased cell proliferation, reduced apoptosis, and cellular enlargement[29]. Independent studies have shown that adult NSCs are regulated by PTEN in the subventricular zone of the lateral ventricles[30].

However, using *in vivo* clonal analysis, researchers found that *Pten* deficiency in quiescent nestin-GFAP-expressing radial glia-like precursor cells in the adult subgranular zone exhausts the pool of these cells, and this is achieved by accelerated terminal differentiation of astrocytes within 30 days[31]. Similarly, another study indicated that *Pten* deletion in adult NSCs results in an increase of the proliferation and differentiation rates of development into hypertrophic neurons. Within several months, the enhanced differentiation rate leads to early exhaustion of the NSC pool. Finally, they showed that mice lacking *Pten* are significantly deficient in social interactions and have infrequent generalized seizures; while more astrocytes, rather than neurons, were derived from newborn cells in the hippocampus after four months of *Pten* deletion[32]. Both studies showed that *Pten* deletion in NSCs initially causes an increase in proliferation and the subsequent exhaustion of NSCs[33] (Fig. 1B).

In vivo experiments showed that NSCs with *Tsc1* deletion increase in size with enlarged vacuoles[34]. The proliferation of NSCs increases with *Tsc1* disruption[35]. In addition, *Tsc1*-null NSCs in the lateral ventricle result in deregulated aggregation and migration[36]. Furthermore, NSCs with *Tsc1* disruption form subependymal nodules and subependymal giant-cell astrocytomas, which are regular characteristics of the TSCs. Furthermore, they found that the loss of *Tsc1* in cultured NSCs does not result in evident changes in morphology or proliferation[36].

Role of the PTEN Signaling Pathway in Dendritic and Synaptic Development

Conditional *Pten* knock-out mice have been used to study Pten in the nervous system[29, 37-41]. Mice with *Pten* deletion in mature neurons of the cerebral cortex and hippocampus have macrocephaly, while the growth of dendrites and axons and the number of synapses are impaired. *In vitro* and *in vivo* studies showed that loss of *Pten* in neurons leads to neuronal hypertrophy with somatic, dendritic, and axonal overgrowth[20, 21]. The dendritic over-growth is further reflected by increased dendritic arborization, increased dendritic caliber, and increased number of dendritic spines. Pten is also involved in the regulation of neuronal polarity; disrupting Pten function leads to multiple ectopic axons and loss of proper axonal projections[20, 42]. Furthermore, Luikart *et al.* recently developed a virus-based strategy that allows *in vivo* knockdown of *Pten* specifically in mouse hippocampal granule cells[43]; they found that granule cells with *Pten* knockdown have a preferential increase in excitatory synaptic functions. A recent study has also shown that Pten overexpression results in reduced spine density, which depends on protein phosphatase activity[44]. Thus, attenuating Pten function in neurons has profound effects on neuronal morphology and circuitry. Interestingly, whether the protein or phospholipid phosphatase activity of Pten contributes to different physiological outcomes needs to be further addressed.

Previous studies have shown that TSC1/2 disruption or hyperactivation of mTORC1 results in neuronal hypertrophy. Importantly, a recent study demonstrated that lack of either TSC1 or TSC2 in neurons also promotes ectopic axon-formation[23, 45]. *Tsc1/2* mutations are suspected to result in mTORC1 overactivation. Thus, it has been proposed that

hyperactivation of the mTOR pathway results in increased synaptic protein synthesis, thereby giving rise to abnormal synaptic function[46].

Role of the PTEN Signaling Pathway in Synaptic Plasticity

To investigate the role of PTEN in mature neuronal circuitry, Chow *et al.* used chronic *in vivo* imaging to trace the changes of pyramidal neurons before and after *Pten* knockout in the cortex of adult mice[47]. They found that the apical dendrites of layers II/III pyramidal neurons in *Pten*-null mice became longer and more tortuous, whereas spine density was significantly reduced along more distal dendritic regions. Interestingly, the apical dendrites of layer V pyramidal neurons in *Pten*-null mice appeared normal, and dendritic growth, spine density, and spine dynamics did not change, suggesting that PTEN plays a distinct role in different neuronal populations in adult circuitry[47] .

Tavazoie *et al.* showed that in the hippocampal pyramidal neurons of rodents, the TSC pathway is essential for the regulation of soma size, dendritic spine density and size, and excitatory synaptic properties[45]. Loss of *Tsc1* leads to increased size but decreased density of dendritic spines. *Tsc1* disruption increases AMPAR-mediated synaptic currents. Neuronal morphology is sensitive to hemizygosity of *Tsc1*. Bateup *et al.* knocked out *Tsc1* in the hippocampal CA1 neurons of mice after birth. They found that metabotropic glutamate receptor-dependent long-term depression, which depends on protein translation, is not detectable in *Tsc1*-knockout neurons[22]. There are no clear abnormalities in dendritic spine number, morphology, or presynaptic release probability with *Tsc1* knockout[22]. This evidence suggests that PTEN and TSC signaling pathways play central roles in the structural and functional plasticity of adult cortical and hippocampal neural circuitry.

Genetic Mouse Models in ASD Studies

Pten knockout mice die in the early embryonic period, and heterozygous mice are susceptible to a variety of tumors, including prostate cancer, endometrial cancer, and lymphoid tumors[48]. *Pten* deletion enhances the proliferation of T-lymphocytes, mammary epithelial cells, NSCs, and astrocytes[29, 40, 49, 50], and hypertrophy is induced in granule neurons, cardiomyocytes, and the cerebellum[38, 51]. Kwon *et al.* ablated *Pten* expression specifically in a subset of post-mitotic neurons in mouse hippocampus and cortex. These mice develop macrocephaly, and display behavioral phenotypes which resemble human autism, including social behavior deficits, seizures, elevated anxiety, and learning deficits[20].

Consistent with the *Pten* deletion phenotypes, knocking out *Tsc1/2* broadly in the brain results in macrocephaly and seizures[23, 24]. In addition, *Tsc2* heterozygous mice with elevated mTORC1 activity in the brain show deficits in learning and memory[52], and *Tsc2* dominant-negative transgenic mice show increased anxiety[53]. Thus, disrupting TSC1/2 complex function in the nervous system mimics the cellular effects of PTEN loss, and loss of *Tsc1/2* in the brain results in behavioral defects similar to PTEN ablation. Together, these data indicate that the TSC1/2 complex is a major component mediating the cellular and behavioral changes observed in *Pten* mutants.

Further studies showed that the specific mTORC1 inhibitor rapamycin can prevent and reverse the enlargement of neurons and improve the abnormal behaviors caused by *Pten* deletion[54]. These results strongly suggest that PTEN-TSC1/2 pathway dysfunction causes autistic phenotypes and correction of the signal pathway reverses some abnormal phenotypes, providing a potential strategy for the treatment of ASDs.

Perspectives and Remaining Questions

Many studies have indicated that the PTEN/TSC/mTOR pathway is involved in the pathogenesis of ASD, although many other pathways could also lead to this complicated syndrome. The regulatory effect of PTEN on NSC development is quite complicated, in that it is not only involved in the regulation of NSC proliferation, but also in the modulation of NSC lineage specification. More importantly, PTEN may play distinct roles in NSC development at different developmental stages and in different stem-cell populations. Is there any evidence indicating that glial cells play any important role in the etiology of ASD? Are there any other suspected ASD genes that affect neuronal differentiation? These questions need to be answered in the mechanistic study of ASDs.

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