REVIEW

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The integral role of *PTEN* in brain function: from neurogenesis to synaptic plasticity and social behavior

Natalia Chwin*, Anna Kiryk

Laboratory of Animal Models, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
** Email: n.chwin@nencki.edu.pl*

The phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) gene is a critical tumor suppressor that plays an essential role in the development and functionality of the central nervous system. Located on chromosome 10 in humans and chromosome 19 in mice, *PTEN* encodes a protein that regulates cellular processes such as division, proliferation, growth, and survival by antagonizing the PI3K-Akt-mTOR signaling pathway. In neurons, PTEN dephosphorylates phosphatidylinositol-3,4,5-trisphosphate (PIP3) to PIP2, thereby modulating key signaling cascades involved in neurogenesis, neuronal migration, and synaptic plasticity. PTEN is crucial for embryonic neurogenesis, controlling the proliferation of neural progenitor cells and guiding the migration and proper lamination of neurons in cortical and hippocampal structures. It also regulates dendritic growth and axon guidance, ensuring correct neuronal connectivity. In postnatal neurogenesis, PTEN maintains the balance of stem cell proliferation and integration of new neurons into existing circuits, particularly in the hippocampal dentate gyrus. Animal models with *PTEN* deletion or mutation exhibit significant structural and functional neuronal abnormalities, including enlarged soma and dendritic hypertrophy, increased synaptic density, and altered synaptic plasticity mechanisms such as long-term potentiation and long-term depression. These changes lead to deficits in learning and memory tasks, as well as impairments in social behaviors. *PTEN* mutations are associated with neurodevelopmental disorders like intellectual disability, epilepsy, and autism spectrum disorders accompanied by macrocephaly. Understanding PTEN's mechanisms offers valuable insights into its contributions to neurodevelopmental disorders and presents potential therapeutic targets for cognitive impairments and neurodegenerative diseases. Future research should focus on elucidating PTEN's functions in mature neurons and its influence on established neuronal networks, which may have significant implications for memory enhancement and behavioral modifications.

Key words: *PTEN* gene, neurogenesis, PI3K-Akt-mTOR pathway, synaptic plasticity, learning and memory, social behavior

INTRODUCTION

Structure and localization of the *PTEN* gene

The phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) gene is located on chromosome 19 in *Mus musculus* and on chromosome 10 in *Homo sapiens* (Hansen & Justice, 1998; Fiuji, 2020). It belongs to a group of tumor suppressor genes that inhibit cellular processes such as division, proliferation, cell growth, and survival. *PTEN* is a highly conserved gene (Fig. 1), and so far, only two of its isoforms, α and β, have been characterized (Taylor & Abdel-Wahab, 2019). The gene contains nine exons, and its main (canonical) transcript encodes a peptide with a mass of 50 kDa, consisting of 403 amino acid residues, with translation starting from the AUG start codon.

The *PTEN* gene encodes two functional domains: catalytic domain located at the N-terminal (amino end) in exon 5, this domain has phosphatase activity, and Ca^{2+} dependent domain (C2) located at the C-terminal (carboxyl end) in exon 7, this C2 domain has an affinity for phospholipid binding.

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Additionally, the gene contains four structural domains, three of which are located at the carboxyl end. Two of polypeptide sequences enriched in proline, glutamate, serin and threonine called PEST domains, regulate protein stability, and the PDZ-binding domain interacts with proteins (e.g., PSD-95), playing a key role in cellular signal transduction. Located at the amino end, the preprotein binding domain (PBD) has binding properties for phosphatidylinositol-4,5-bisphosphate (Fig. 1) (Waite & Eng, 2002; Hopkins et al., 2014). Under physiological conditions, the PTEN protein is found in the cell nucleus, the nuclear envelope, and at lower concentrations in the cytoplasm. The protein structure includes NLS motifs (nuclear localization signals) and NES motifs (nuclear export signals). After PTEN protein synthesis in the cytoplasm, NLS motifs are recognized by specific proteins that transport PTEN to the nucleus, while NES motifs are involved in exporting PTEN from the nucleus to the cytoplasm (Ho et al., 2020).

For the α and β isoforms, translation starts from alternative initiation codons located in the untranslated region (UTR) at the 5' end of the transcript. The resulting peptides are longer by an additional 146 and 173 amino acid residues for the PTEN α and β transcripts, respectively. Literature suggests that these alternative PTEN proteins may function as oncogenes, although their exact roles are not yet well understood (Taylor & Abdel-Wahab, 2019).

Under physiological conditions, PTEN is a flexible protein with strong intramolecular interactions and undergoes conformational changes resulting from post-translational modifications (Song et al., 2012; Bassi et al., 2013). Conformational changes also occur during interactions with substrates. In neurons, the PTEN protein is located in the cell nucleus and in the cytoplasm of dendritic spines and axon terminals. The nuclear function of PTEN is associated with the differentiation and survival of developing neurons during neurogenesis. (Lachyankar et al., 2000; Kreis et al., 2014). Studies have also shown that PTEN concentration in mature neurons increases in the nucleus during traumatic brain injury and during excitotoxicity activated by NMDA receptors (Goh et al., 2014; Lai et al., 2014). In developing neurons, cytoplasmic PTEN regulates neuronal polarization, migration, and the growth of axons and dendrites. In mature neurons, PTEN is involved in neuroplastic processes (Kreis et al., 2014).

Intracellular signaling cascade of PTEN/PI3K-Akt-mTOR pathway

The primary target of PTEN phosphatase is the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3), which mediates the activation of the PI3K-Akt-mTOR signaling pathway (Endersby & Baker, 2008). In the cytoplasm, PTEN inhibits this pathway by dephosphorylating PIP3, converting it into PIP2 (phosphatidylinositol-4,5-bisphosphate). PTEN functions as an antagonist to phosphatidylinositol 3-kinase (PI3K), a lipid kinase that phosphorylates the inositol ring of phosphatidylinositol at the 3-hydroxyl position of PIP2, a component of the cell membrane (Stambolic et al., 1998; Stocker et al., 2002). This reaction produces PIP3, which recruits various signaling proteins to the membrane.

An increase in cellular PIP3 levels due to PI3K activity leads to the activation of signaling proteins containing a pleckstrin homology (PH) domain, which binds PIP3 at the membrane. One of the main effectors of PI3K is the kinase Akt, also known as protein kinase B (PKB). Activation of Akt kinase occurs *via* its

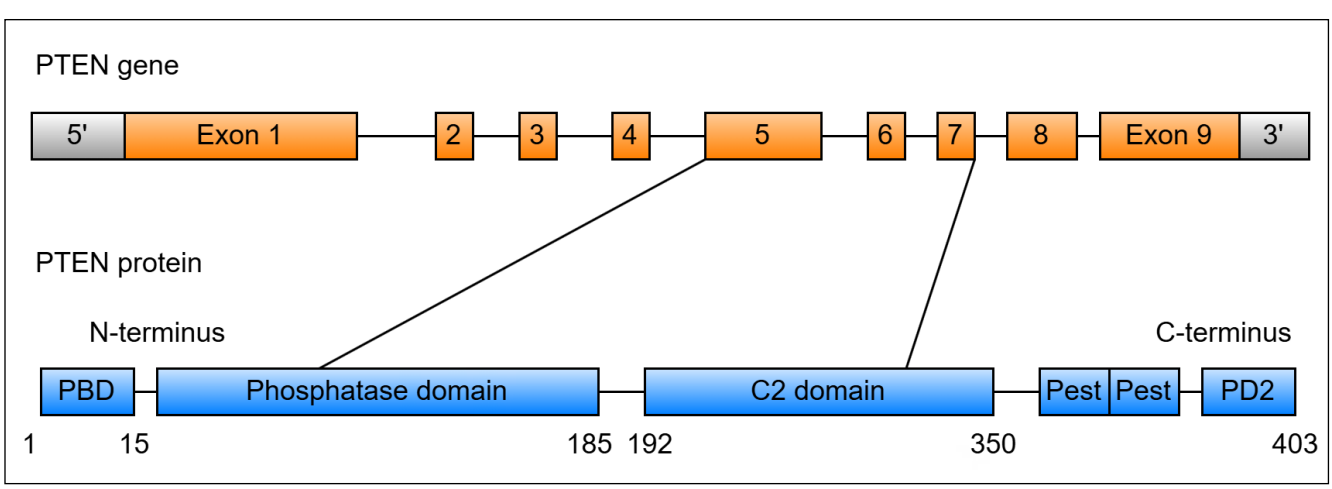

Fig. 1. Schematic representation of canonical *PTEN* gene (upper part) and protein structure (lower part).

recruitment to the plasma membrane and subsequent phosphorylation at threonine 308 by phosphoinositide-dependent kinase 1 (PDK1) and at serine 473 by the mTORC2 complex (Sarbassov et al., 2005; Manning & Toker, 2017). Activated Akt kinase phosphorylates multiple proteins in the central nervous system involved in neuronal growth, proliferation, survival, and synaptic plasticity, which underpin learning and memory (Graber et al., 2013; Saxton & Sabatini, 2017).

One of Akt's target substrates is the ubiquitous serine/threonine kinase mTOR (mammalian target of rapamycin). mTOR is highly conserved across mammalian cell types but occupies a unique role in neurons (Saxton & Sabatini, 2017). mTOR functions within two distinct protein complexes, mTORC1 and mTORC2, which differ in their sensitivity to rapamycin and its derivatives (Hay & Sonenberg, 2004; Wullschleger et al., 2006). Biochemically, these complexes differ in protein composition: both contain mTOR, Deptor, and mLST8; however, Raptor and PRAS40 (proline-rich Akt substrate of 40 kDa) are unique to mTORC1, while Rictor, Protor, and Sin1 are specific to mTORC2.

The function of mTORC1 is much better understood than that of mTORC2. mTORC1 regulates neuronal growth and proliferation by phosphorylating two key substrates: S6 kinases (S6Ks) and eukaryotic initiation factor 4E-binding proteins (4E-BPs) (Hoeffer & Klann, 2010). Activated mTORC1 can also initiate a negative feedback loop by phosphorylating insulin receptor substrate-1 (IRS-1) *via* S6K1, thereby attenuating upstream signaling (Shah & Hunter, 2006).

Both mTORC1 and mTORC2 are activated during synapse formation and modulate synaptic plasticity by regulating the responses of pre- and postsynaptic neurons to neurotransmitters released into the synaptic cleft (Henry et al., 2012; Sun et al., 2016; McCabe et al., 2020; Seo et al., 2020). Studies indicate that mTORC1 is directly involved in synthesizing proteins essential for the formation and stabilization of synaptic connections, especially during long-term potentiation (LTP) (Fingar et al., 2004; Magri et al., 2013). In contrast, mTORC2 regulates the actin cytoskeleton, crucial for maintaining the structure and plasticity of dendritic spines during both LTP and long-term depression (LTD) (Huang et al., 2013; LaSarge & Danzer, 2014).

The specific roles of mTORC1 and mTORC2 in glutamatergic transmission during learning are not fully elucidated and remain active areas of research. Studies on cultured mouse hippocampal neurons suggest that mTORC1 modulates synaptic transmission at postsynaptic terminals, whereas mTORC2 controls the release of neurotransmitter vesicles at presynaptic terminals of glutamatergic neurons (McCabe et al., 2020). mTORC1 and mTORC2 have opposing effects on synaptic vesicle fusion with the plasma membrane: active mTORC2 enhances vesicle release to the postsynaptic density (PSD), whereas activated mTORC1 reduces the number of vesicles released. mTOR regulates cell and dendrite size *via* both complexes (Saci et al., 2011; Urbanska et al., 2012; Ragupathi et al., 2024).

In summary, the PTEN phosphatase functions as a guardian of cellular homeostasis by inhibiting the PI3K-Akt-mTOR pathway. In the hippocampal formation, PTEN controls the development and maturation of neurons during both early and late neurogenesis, as well as the morphology and functionality of mature neurons (Amiri et al., 2012; LaSarge et al., 2015; Latchney et al., 2023; Luan et al., 2023).

Role of PTEN in brain development and neurogenesis

Neuronal morphology and functionality

Silencing the *PTEN* gene results in molecular changes primarily due to deregulation of the PI3K-Akt pathway and subsequent downstream regulation of pathways controlled by Akt kinase (Rashid et al., 2018; Singh & Singh, 2020; Guo et al., 2024). These molecular alterations, manifesting as disrupted cellular homeostasis, also lead to structural and functional changes in both developing and mature neurons. Germline mutations in *PTEN* are associated with various human diseases, ranging from different cancer types in somatic cells to conditions categorized as PTEN-hamartoma tumor syndromes (PHTS) resulting from inherited dominant mutations of the *PTEN* gene (Tan et al., 2012). Germline mutations in *PTEN* have also been identified in a subset of patients with neurodevelopmental and neurological disorders such as intellectual disability, epilepsy, or autism spectrum disorders accompanied by macrocephaly (Courchesne et al., 2003;Butler et al., 2005; McBride et al., 2010; Bubien et al., 2013; Rademacher & Eickholt, 2019). Furthermore, experiments using various transgenic models with *PTEN* deletion have demonstrated that the functional diversity of mutations and genetic background significantly affect the spectrum of phenotypes observed (Table 1) (Kwon et al., 2006; Sperow et al., 2012; Takeuchi et al., 2013; Smith et al., 2016; Wang et al., 2017).

Neurogenesis

Studies on rodents have shown that *PTEN* plays a key role in embryonic neurogenesis, as germline animal models with *PTEN* gene deletion are lethal, and heterozygous mice with a *PTEN* gene mutation exhibit an

altered phenotype, such as cortical and hippocampal hypertrophy, resulting from increased proliferation of progenitor cells (Di Cristofano et al., 1998; Page et al., 2009; Clipperton-Allen & Page, 2014). In the embryonic mouse brain, hippocampal neurogenesis starts around E10, and the peak of neurogenesis occurs between E14 and E18, during which PTEN expression is not present, and probably the absence crucial for cell division, and proliferation (Hayashi et al., 2015; Bond et al., 2020). However, PTEN participates in the proper lamination of cortical and hippocampal structures and guides the migration of young neurons (Garcia-Junco-Clemente & Golshani, 2014). The migration of pyramidal neurons and interneurons starts between E12-18, while on E17.5, progenitor granule cells begin migrating to the dentate gyrus (DG) and eventually reach it around postnatal day 14 (P14) (Bond et al., 2020; 2022; Kitazawa et al., 2014). Pyramidal neurons form in the ventricular zone (VZ) of the developing brain, located near the lateral ventricles, and migrate radially along glial fibers, which act as scaffolding guiding them to hippocampal subregions, where they integrate into neuronal networks. Granule cell precursors, meanwhile, migrate through the fimbria to the DG (Galceran et al., 2000; Xu et al., 2015). Furthermore, GABAergic immature interneurons have yet another migration route. They form in the medial ganglionic eminence (MGE) and migrate tangentially through the developing neocortex, eventually reaching hippocampal areas and integrating with local circuits (Pleasure et al., 2000). The loss of *PTEN* during neurogenesis disrupts this process, causing ectopic distribution of hippocampal neurons (Amiri et al., 2012). Additionally, it has been shown that once neurons settle in the hippocampal formation, PTEN modulates cytoskeletal dynamics, ensuring controlled dendrite growth and axon guidance, while neurons lacking PTEN expression exhibit excessive dendritic branching and misdirected axons, leading to connectivity impairment (Kreis et al., 2014; Kath et al., 2018). These features have been observed in most constitutive mouse models with *PTEN* deletion and conditional models where *PTEN* was removed at an early stage of embryogenesis, or from hippocampal stem/precursor cells at the postnatal stage, or before the completion of synaptogenesis and stabilization of connections in the cortico-hippocampal network (Table 1). Additionally, *PTEN* deletion models may exhibit hyperphagia and disrupted electrophysiology resulting from synapse or neuron overgrowth (Bajenaru et al., 2002; Kwon et al., 2003; Lugo et al., 2014). During postnatal neurogenesis, PTEN maintains proper proliferation of granule cells in the subventricular zone (SVZ), also influencing the generation of interneurons migrating to the olfactory bulb (Zhu et al., 2012). In the hippocampus, it controls neurogenesis in the subgranular zone (SGZ) of the dentate gyrus, ensuring the integration of newly formed granule cells into hippocampal circuits (Latchney et al., 2023). Impairment of *PTEN* in the postnatal period leads to delayed cell maturation in the SGZ layer and can also disrupt the axonal structure of mossy fibers, which may affect the proper stimulus flow through the trisynaptic circuit during learning and memory formation (LaSarge et al., 2015).

Role of PTEN in synaptic plasticity and learning

In the central nervous system, the opposing activity of PTEN/PI3K also plays a crucial role in modulating synaptic strength and plasticity (Fig. 2). Synaptic plasticity is the brain's ability to modify synaptic strength and efficiency of synaptic connections between neurons in response to a changing environment. The fundamental molecular mechanisms underlying learning and memory formation are long-term potentiation (LTP) and long-term depression (LTD) (Stacho & Manahan-Vaughan, 2022). PTEN regulates synaptic formation and stability, which ensures proper neuronal connectivity by preventing aberrant structural overgrowth (Fig. 2). The role of PTEN in neuronal morphology and synapse regulation was shown in *PTEN* knockout animal models (Table 1) (Backman et al., 2001; Kwon et al., 2003; 2006). PTEN influenced the structure and function of neurons, including soma and dendritic hypertrophy, as well as the formation of axonal tracks and spine density in conditional deletion models (Amiri et al., 2012; Kwon et al., 2006). Synaptic changes observed in mouse models with *PTEN* deletion vary and depend on factors such as the area where the mutation occurred, the neuronal population, and the age of the animals. In conditional *PTEN* knockout models, particularly in differentiating neurons (GFAP-Cre), seizures accompanied by progressive macrocephaly and decreased lifespan have been observed (Backman et al., 2001; Kwon et al., 2001; 2003). Additionally, the mice exhibit hyperactive behavior and impaired cognitive functions due to structural deficits (Hodges et al., 2018; Lugo et al., 2014). In *PTEN*-deleted hippocampal regions, there was evidence of increased synaptic density, larger excitatory synaptic sites, and enhanced AMPA receptor activity, which are essential for synaptic plasticity (Fig. 2) (Williams et al., 2015). In contrast, *PTEN* deletion in CaMKII-Cre driving line, neurons do not affect hippocampal structure and have not promote overgrowth of cell (soma size) and nucleus size. Dendritic and axonal width, length and thickness parameters were normal, and no changes have been observed in neuronal arborization. However, it has been observed decreased performance in spatial and object-recognition tasks,

Table 1. The role of *PTEN* gene in learning, memory, and social behaviors.

PTEN gene modification	Animal Model	Neuronal morphology	Behavioral tasks	Major results	Authors
Constitutive missense mutation of PTEN isoform alpha	PTENα$^{mu/mu}$	Normal hippocampus and cortex cells	CFC, MWM	Improved recall memory (CFC), diminished memory recall, as indicated by reduced time spent in the target quadrant (phenotype rescued by exogenous LV-PTEN administration), normal locomotor activity	(Wang et al., 2017)
Conditional deletion in forebrain excitatory postnatal neurons	PTEN$^{loxP/loxP}$ CaMKIIαCre	normal	MWM	7–8-week-old mice: spatial training session: no difference, hidden platform test: less time spent, decreased LTP and LTD, shorter lifespan	(Sperow et al., 2012)
Conditional deletion (cortex, hippocampus, cerebellum)	PTEN$^{loxP/loxP}$, GFAP-Cre	ncba	3 chamber, marble burying, OF, EPM, USV test	Hyperactive behavior, decreased anxiety, impairment in social behavior, deficits in repetitive behaviors	(Lugo et al., 2014)
		cell-autonomous hypertrophy in granule cell in cerebellum and DG	ncba	Seizures and ataxia, progressive macrocephaly and premature death	(Kwon et al., 2003)
		granule-cell dysplasia in the cerebellum and DG	ncba	Seizures and ataxia, progressive macrocephaly, hippocampus neurodegeneration and premature death	(Backman et al., 2001)
		ncba	CFC, cue FC, TFC	Cue FC – no difference between genotypes, decreased recall about aversive event in CFC and TFC	(Lugo et al., 2013)
Conditional deletion	PTEN$^{loxP/loxP}$ GFAP-Cre (NS-Pten)	ncba	NOR, Lashley maze	Worsen learning and memory	(Hodges et al., 2018)
Conditional deletion in neuronal populations (cerebral cortex, hippocampal formation-DG and CA3)	PTEN$^{loxP/loxP}$ Nse-Cre; Rosa26R	Soma, dendritic hypertrophy, and thickness, hypertrophic and ectopic axonal track with increased synapses and spine density	OF, EPM, dark/light boxes test, MWM, context and cue FC	At 4 weeks of age, hyperactive behavior, decreased anxiety in EPM but increased during exposition to light conditions, Worsen learning and memory, no differences in context and cue FC, reduced lifespan	(Kwon et al., 2006)
Inducible deletion in hippocampal neuronal stem/ progenitor cells (SGZ and SVZ) at 4 weeks of age	PTEN$^{loxP/loxP}$ Nestin-CreER^{T2}	Progressive hypertrophy (axon, dendrites), and ectopic axonal tracts, increased thickness of mossy fiber tract, adult hippocampal NSC neurogenesis: higher proliferation and differentiation rate	OF, Rotarod test, SIT	Macrocephaly, seizures, decreased social interactions, after 4-5 months of KO induction: Hyperactive behavior and resistant to handling	(Amiri et al., 2012)
Conditional deletion in DA neurons	PTEN$^{loxP/loxP}$, DAT-Cre	ncba	3 chamber, cue and context FC	Sex-difference changes during freezing behavior in FC and sociability test (males – normal behavior, females – lack of distinguish between object *vs.* mouse), social novelty – both sexes developed no preferences for social novelty	(Clipperton-Allen & Page, 2014)
Inducible deletion in DG at P7	PTEN$^{LoxP/loxP}$ + retrovirus (pRubi-mCherry-T2A-Cre)	Soma hypertrophy, neurons with increased dendritic outgrowth and protrusions, Filopodia precede increased mushroom spine density	ncba	Increased markers of activity in developing neurons, increased drive was due to an increase in the number and size of glutamatergic currents, increased synaptic depolarization of PTEN KO neurons is due primarily to the increased number of excitatory synaptic sites, increased amplitude of quantal-like aEPSCs (as for mEPSCs), increase number of synaptic AMPA receptors	(Williams et al., 2015)

(DA) DOPAminergic neurons, (DAT) dopamine transporter, (MWM) the Morris water maze test, (FC) fear conditioning, (CFC) contextual fear conditioning test, (TCT) trace fear conditioning test, (mu) mutation, (EPM) the elevated plus maze test, (OF) open field test, (ncba) not checked by author, (NOR) novel object recognition, (SIT) social interaction test (social target *vs.* inanimate object), (P7) postnatal day 7, (LV) lentivirus.

reduced synaptic plasticity (e.g., LTP and LTD), and impaired recall in fear-conditioning paradigms (Sperow et al., 2012; Wang et al., 2017). Constitutive missense mutations improved recall memory in some tasks but weakened it in others, depending on the experimental context, suggesting PTEN's subtle involvement in memory encoding and retrieval (Wang et al., 2017). However, inducible *PTEN* deletion limited to a single structure or

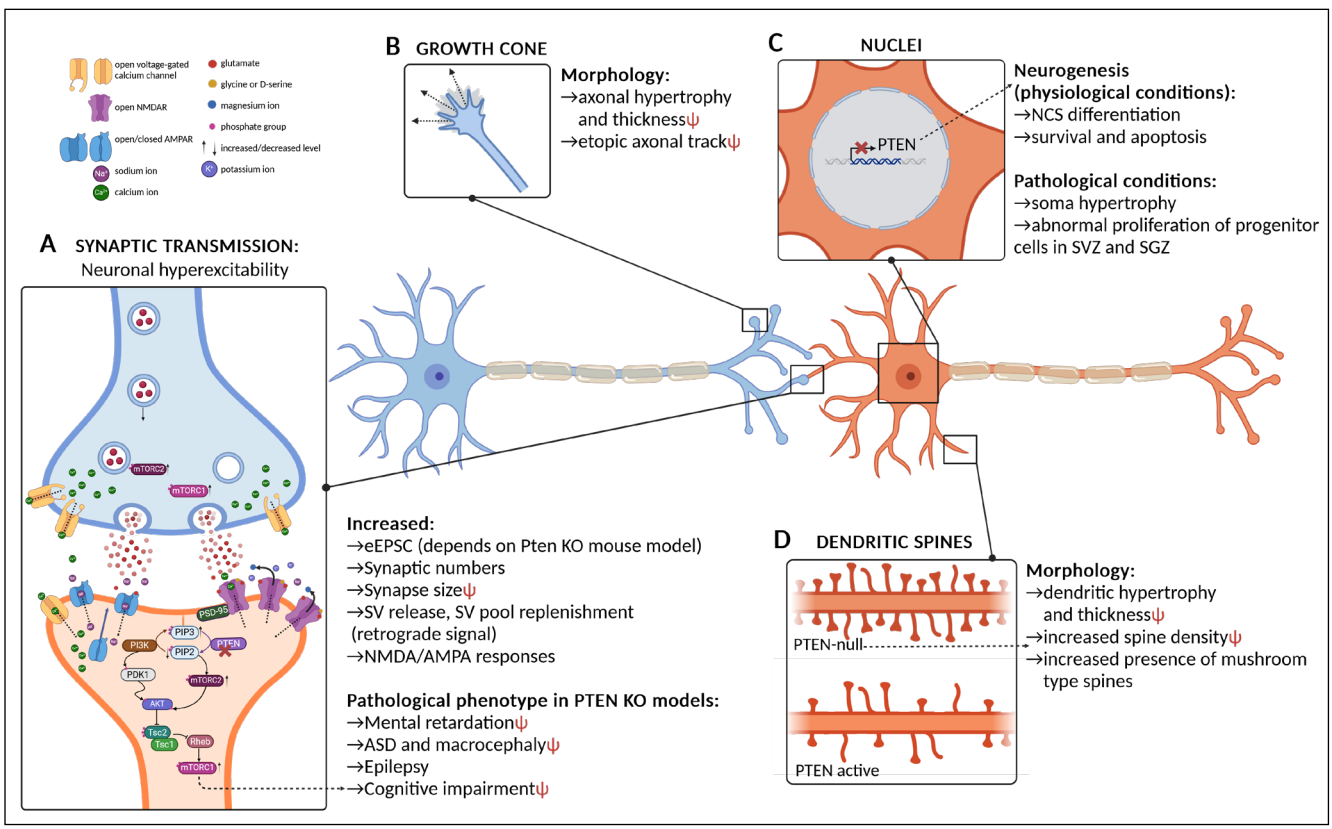

Fig. 2. Localization and role of PTEN in neuronal development, synaptic function, and structural plasticity based on studies with PTEN inhibition or knockout. (A) A schematic representation of abnormal synaptic transmission in hyperactive glutamatergic neurons due to PTEN absence. The lack of PTEN increases PIP3 in the postsynaptic membrane, which is important during NMDAR-dependent LTP activation. PIP3 indirectly, through PDK1, activates the Akt-mTOR signaling cascade. Active mTOR is involved in the transcription and synthesis of several effector genes, which are necessary to maintain the continuity of the synaptic strengthening process. PTEN absence increases long-term PI3K-Akt-mTOR activity and, for instance, can cause a constant Ca^{2+} influx by release from the endoplasmic reticulum and increased AMPA receptor trafficking to the postsynaptic membrane. Additionally, increased expression of mTORC1 and mTORC2 can induce neurotransmitter release from synaptic vesicles (SVs) in the presynaptic membrane and SV replacement through a retrograde signal, the mechanism of which is not fully understood. (B) During neuronal development, PTEN is enriched in the axons and dendrites and modulate the dynamics in growth. Absence of PTEN in growth cone during axonal navigation, increases abnormal distribution of neurons and improper neuronal connections which affect social memory and cognitive functions. (C) Nuclear PTEN has been described to regulate neuronal survival or specifically induces apoptotic responses. Movement to the nucleus has been reported during traumatic brain injury or degeneration; however, the mechanism is not fully understood. Moreover, during embryonic neurogenesis, lack of PTEN expression until around P0 in neuronal nuclei is physiological and stimulates neuronal stem cells (NSC) for differentiation into immature neurons. However, PTEN expression occur during postnatal and adult neurogenesis, when progenitor and young neurons migrating from the SVZ and SGZ to proper structures. Absence of PTEN during this process can affect neuron morphology. (D) In mature CNS neurons PTEN is found in the dendrite. During NMDAR-dependent dendritic spine plasticity – long tern depression (LTD), PTEN translocates deep into the spine and anchors to the postsynaptic density by binding with PDS-95. PTEN, by targeting membranous PIP3, participate in the dynamic changes in spine morphology during synapse development and plasticity. PTEN absence is contributes to generating a higher number of spines with mushroom shaped heads. PTEN mutation or inhibition before establishment of functional neuronal network, affects morphology as well structural and functional plasticity, which contribute to neurodevelopmental disorders such as autism, epilepsy, and mental retardation. (The Fig. 2A represents only a fragment of the synaptic transmission process, focusing on the role of PTEN and the activated pathway, while in cases B, C, and D, the exact mechanism of action is not yet fully understood). Akt-protein kinase B, (AMPA) amino-3-hydroksy-5-methyl-4-isoxazolepropionic acid, (NMDA) N-methyl-D-aspartate receptor, mTOR-mammalian target of rapamycin, (PDK1) pyruvate dehydrogenase kinase 1, (PIP3) phosphatidylinositol (3,4,5)-trisphosphate, (PI3K) phosphoinositde 3-kinase, (PSD-95) postsynaptic density 95, Rheb-Ras homolog enriched in brain, (Tsc1/Tsc2) tuberous sclerosis 1 and 2. Ψ- processes which mostly appearing in PTEN-null progenitor and immature neurons during embryonic and postnatal neurogenesis before developing of functional connections between neurons and progenitor cells in subgranular zone (SGZ) and subventricular zone (SVZ) where the adult neurogenesis occurs.

neuronal population revealed mild changes compared to conditional knockouts and showed different results. Some inducible *PTEN* knockout models and in vitro studies demonstrated normal neuronal morphology and increased excitatory currents and quantal amplitudes. These models have not been behaviorally tested for learning and memory formation (Table 1) (Luikart et al., 2011; Williams et al., 2015).

Role of PTEN in social behaviors

In *PTEN* deletion models, social deficits were detected using various social tasks (Table 1). Conditional deletion of *PTEN* in the cortex, hippocampus, and cerebellum led to impairments in social behavior. Mice showed reduced sociability, as evidenced in tasks like the 3-chamber test, which measures preference for social interaction (Lugo et al., 2014). Inducible deletion of *PTEN* in hippocampal neuronal stem/progenitor cells resulted in decreased social interactions. These mice also exhibited hyperactivity and resistance to handling after four to five months of knockout induction (Table 1) (Amiri et al., 2012).

Sex-specific social effects were found by Clipperton-Allen & Page, 2014. Conditional deletion of *PTEN* in dopaminergic (DA) neurons demonstrated sex-specific changes in social behavior, namely lack of the ability to distinguish between objects and mice in females, but normal sociability in males. However, both sexes failed to develop preferences for social novelty, suggesting PTEN's broad role in modulating social interactions, potentially through dopaminergic circuits.

Disturbances in social interactions could be related to hyperactive behavior and altered anxiety levels observed in various *PTEN* deletion models (e.g., Kwon et al., 2006; Lugo et al., 2014). Increased activity and stress responses could make it difficult for mice to engage appropriately in social tasks. Also, altered neuronal morphology (e.g., hypertrophy, ectopic synapses, and increased spine density in cortical and hippocampal neurons) may be related to social impairments.

CONCLUSIONS

The *PTEN* gene is integral to the development and functionality of the central nervous system. Its dual role in tumor suppression and synaptic plasticity presents a complex interplay of molecular pathways with significant implications for neurological health. PTEN is critical for maintaining the balance of synaptic plasticity and proper neuronal function. Dysregulation of *PTEN*, either by deletion or mutation, disrupts synaptic architecture, plasticity mechanisms (like LTP/LTD), and cognitive abilities, leading to behavioral abnormalities and impairments in learning and memory (Fig. 2). Moreover, PTEN plays a significant role in regulating social behaviors, with its deletion leading to marked deficits in social interactions, novelty recognition, and sex-specific sociability. These effects are likely mediated through changes in synaptic architecture and neural activity within social behavior-related brain circuits, such as the hippocampus, cortex, and dopaminergic pathways. Future research should focus on elucidating PTEN's contributions to neurodevelopmental disorders and exploring its therapeutic potential in targeting cognitive impairments and neurodegenerative diseases. Additionally, it is important to investigate PTEN's function in fully differentiated neurons, as evidence suggests that *PTEN* mutations in distinct hippocampal structures, such as the dentate gyrus, enhance LTP and neuronal excitability. This could directly contribute to improved learning in the mature brain and may have therapeutic applications for individuals with memory-related issues. It would also be worthwhile to examine whether the removal of *PTEN* in a stabilized neuronal network could induce behavioral changes once perception and personality traits are already established. Could the deletion of a single gene, for instance, shift an extroverted individual toward introversion?

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