Review Article

Yanchao Lu, Ying Gao, Ranran Chen, Shumin Zhao, Jialing Liu, Sutian Zhang, Xue Bai* and Jingjing Zhang*

Pumilio 2 in neural development, function, and specific neurological disorders

https://doi.org/10.1515/med-2025-1332
Received April 15, 2025; accepted October 10, 2025;
published online December 17, 2025

Abstract

Introduction: Pumilio 2 (PUM2) is an evolutionarily conserved RNA-binding protein that recognizes and binds to the 5′-UGUAXAUA-3′ motif in target mRNAs via its C-terminal domain, thereby reducing mRNA stability and translation efficiency. Recent evidence indicates that PUM2 plays a critical role in nervous system development and function, and its dysregulation contributes to the pathogenesis of certain CNS disorders.

Content: Based on a comprehensive review of existing literature on PUM2and the nervous system in PubMed, this article provides a concise overview of recent advances in understanding the role of the PUM2 protein in central nervous system (CNS) development and disease.

Summary: PUM2 is highly expressed in the central nervous system (CNS), where it regulates nervous system development by participating in neurogenesis and neuronal migration, the differentiation and maturation of neuronal subtypes, and the growth of dendrites and axons. Furthermore, in the mature CNS, PUM2 modulates synaptic types and excitability, regulates the expression of voltage-gated sodium channel proteins, Na+ channel density, neurotransmitter degradation and postsynaptic receptor expression, participates in the regulation of normal nerve signal conduction, and thereby impacts normal nervous system physiology as well as contributing to the pathogenesis of diverse neurological disorders such as epilepsy, stroke, and glioma.

Outlook: This article aims to deepen the understanding of the function of Pumilio2 protein in the nervous system, and hopes to provide new research directions and theoretical support for the treatment strategies of neurological diseases.

Keywords: Pumilio 2; nervous system; dendrites axons; excitability; neurological disorders

Introduction

The Pumilio (Pum) protein family constitutes a class of evolutionarily highly conserved RNA-binding proteins (RBPs) that regulate protein translation and expression by recognizing and binding target nucleic acids via conserved Pumilio homology domains [1]. Genome-wide studies have identified over 4,000 mammalian mRNAs subject to direct or indirect regulation by this family. Pum protein was first discovered in fruit flies and *Caenorhabditis elegans*, where they play critical roles in embryonic development and germ cell formation [2]. Unlike other RNA families with hundreds of members, the Pum protein family comprises only two members, PUM1 and PUM2, which are highly homologous and are important for maintaining genomic integrity.

Xue Bai and Jingjing Zhang share senior authorship. The idea for this review topic was conceived by Xue Bai and Jingjing Zhang, who also contributed to revising the manuscript. Yanchao Lu, as the first author, was responsible for designing and writing the manuscript as well as drawing the charts. Ying Gao, Ranran Chen, Shumin Zhao, Jiangling Liu, and Sutian Zhang took part in the article writing discussion and were involved in drafting and modifying the figure. All authors made contributions to revising the manuscript and approved the submitted version.

***Corresponding authors: Xue Bai and Jingjing Zhang**, Department of Neurology, Medical Research Center, Chifeng Municipal Hospital, Chifeng Clinical Medical College of Inner Mongolia Medical University, Hada Subdistrict, Hongshan District, Chifeng City, Inner Mongolia, 224000, P.R. China, E-mail: 1036516668@qq.com (X. Bai), 45590877@qq.com (J. Zhang). https://orcid.org/0009-0005-9996-708X (X. Bai)

Yanchao Lu, Ying Gao, Ranran Chen, Shumin Zhao, Jialing Liu and Sutian Zhang, Department of Neurology, Medical Research Center, Chifeng Municipal Hospital, Chifeng Clinical Medical College of Inner Mongolia Medical University, Chifeng City, Inner Mongolia, P.R. China, E-mail: 1789127221@qq.com (Y. Lu), 1829770600@qq.com (Y. Gao), 168655076@qq.com (R. Chen), 1529503482@qq.com (S. Zhao), 2501191271@qq.com (J. Liu), 15584905205@163.com (S. Zhang). https://orcid.org/0009-0000-0426-2559 (Y. Lu). https://orcid.org/0009-0006-7573-1619 (Y. Gao). https://orcid.org/0009-0001-3198-0895 (R. Chen). https://orcid.org/0009-0009-6433-576X (S. Zhao). https://orcid.org/0009-0006-2603-813X (J. Liu). https://orcid.org/0009-0007-2310-9999 (S. Zhang)

In mammals, *PUM2* is expressed in multiple organ systems including nervous, cardiovascular, digestive, musculoskeletal, hematopoietic, and reproductive systems, but exhibits highest levels in the brain and testes, where it is involved in the growth, development, and maintenance of these systems. Both PUM2 and PUM1 proteins bind thousands of mRNAs, specifically including at least 694 target genes implicated in axonal guidance, synaptic plasticity, and neurotrophic signaling pathways [3], pathological alterations in these pathways are strongly associated with neurological disorders [4]. Experimentally, silencing *PUM2* and *PUM1* significantly reduced the number of neural stem cells in the postnatal hippocampus dentate gyrus, increased perinatal cell apoptosis, changed the composition of dentate gyrus cells, and impaired learning and memory ability. This article provides a brief review of recent advances in the role of the PUM2 protein in central nervous system (CNS) development and disease.

Literature search and screening

Studies included in this review were required to meet three criteria [1]: original research elucidating PUM2's molecular mechanisms [2]; employment of CNS-relevant *in vivo* or *in vitro* models [3]; English-language publications with complete datasets. Letters to the editor and articles lacking comprehensive research data were excluded. Primary literature searches were conducted through PubMed using the Boolean query: (*Pumilio2* OR *PUM2* OR "*Pumilio homolog 2*") AND ("central nervous system" OR CNS OR neurodevelopment OR "neurological disorders" OR pathogenesis). All retrieved records were imported into EndNote 20 for deduplication and management. Following initial title/abstract screening against inclusion criteria, full-texts of candidate studies underwent secondary evaluation. Relevant data regarding *PUM2*'s functions in neural development and pathogenesis were systematically extracted.

The molecular structure and function of PUM2

PUM2 is a~114 kDa protein encoded by the *PUM2* gene, which spans >80 kb across 20 exons on chromosome 2p23-24. This evolutionarily conserved protein is ubiquitously expressed across eukaryotes – from yeast to mammals and plants. PUM2 protein exhibits high evolutionary conservation across species, reflected in its structurally conserved domains. The C-terminus invariably contains a 361-amino acid Pumilio homology domain (PUM-HD) comprising eight tandem imperfect repeats of 36 residues each. Each repeat folds into three α-helices – two elongated helices flanking a shorter central helix – that collectively form a crescent-shaped RNA-binding scaffold. These repeats stack through hydrophobic interfaces to establish the canonical PUM-HD tertiary structure, enabling sequence-specific RNA recognition [5]. Critically, each repeat unit engages in nucleotide-specific interactions with a cognate base within the 8-nt Pumilio-binding element (5′-UGUAXAUA-3′), collectively enabling high-affinity mRNA binding that drives translational repression [6]. The N-terminal domain of PUM2 protein constitutes a low-complexity, intrinsically disordered region enriched in serine, glutamine, and alanine residues. This phylogenetically conserved module shows no significant homology to other known protein domains [7]. Three conserved repressor domains (RDs) within the N-terminal low-complexity region mediate mRNA expression downregulation, though their precise mechanistic basis remains unresolved [8](Figure 1). The crystal structure of PUM2 reveals 292 distinct RNA-binding interfaces, underpinning its capacity to regulate thousands of distinct mRNAs within the nervous system [9]. As an RNA-binding protein, PUM2 could mediate post-transcriptional repression of transcripts through various mechanisms. For example, it could directly recruit CCR4-POP2-NOT (an exonuclease) to function, leading to translational inhibition and mRNA degradation [10]; it could promote the accessibility of miRNAs and thereby trigger repression that is independent of deadenylation; it could also specifically recognize and bind mRNAs containing PBE through its C-terminal Pumilio homology domain, reducing their translation speed and efficiency [11]. Additionally, PUM2 protein plays important roles in many other aspects beyond post-transcriptional regulation, such as suppressing gene programs necessary for maintaining genomic stability, regulating cellular cytosolic sensing of virus infection, and promoting the proliferation of stem cells [12].

PUM2 is involved in the development of the nervous system

The vertebrate nervous system, comprising the central (CNS) and peripheral (PNS) divisions, arises from embryonic ectoderm through neural tube closure and neural crest delamination. The human CNS undergoes four cardinal developmental processes: neural progenitor generation, neuronal migration, synaptogenesis, and myelination during embryogenesis and postnatal maturation [13]. PUM2 protein regulates central nervous system (CNS) development by orchestrating neurogenesis and synaptogenesis (Figure 2).

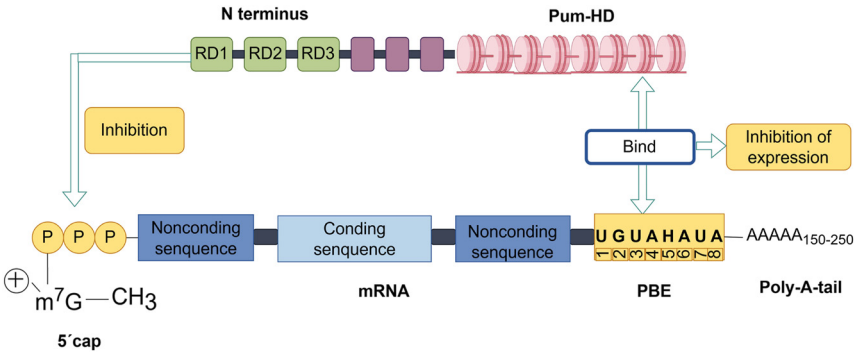

Figure 1: Structural and functional architecture of Pum1/2 repression machinery. PUM2 is a 114 kDa protein encoded by a gene with 20 exons. At the C-terminus, PUM2 contains a typical Pumilio homology domain (HD) that recognizes and binds to mRNA containing the 5′-UGUAXAUA-3′ Pumilio binding element (PBE) to repress its translation. At the N-terminus, PUM2 has three RD inhibitory domains that could reduce the expression level of the target mRNA (Schematics were created using [Figdraw] and are licensed under a paid subscription. All elements were designed de novo by the authors based on established molecular mechanisms).

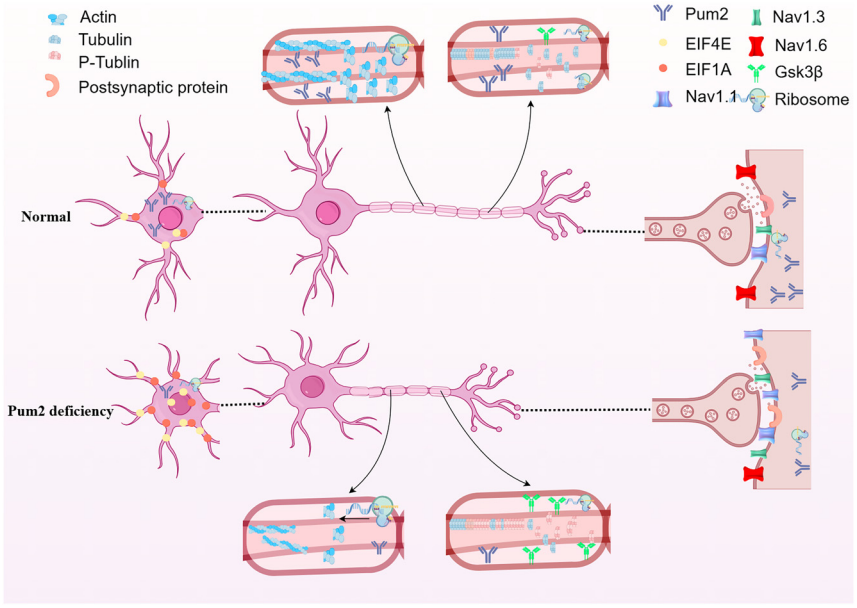

Figure 2: PUM2 regulatory network in neuronal development. In the normal state, PUM2 suppresses the expression of EIF1A and EIF4E and dendritic growth, promotes axonal growth by regulating the expression of glycogen synthase kinase 3β (Gsk3ß) and cell adhesion molecule (Llcam) within axons, and controls synaptic function by downregulating the expression of synaptic-related proteins and Nav1.1 and Nav1.3 channels while upregulating the expression of Nav1.6. The above results are reversed in the absence of PUM2 (Schematics were created using [Figdraw] and are licensed under a paid subscription. All elements were designed de novo by the authors based on established molecular mechanisms).

PUM2 regulates neural development and migration

Neurogenesis is a comprehensive process, encompassing the proliferation of neural stem cells and their balanced and unbalanced divisions to become committed progenitor cells, the gradual migration to functional regions, continuous plastic changes, and the establishment of synaptic connections with other neurons to generate neural functions. During this process, the PUM2 protein promotes the generation and differentiation of neurons, thereby driving the process of neurogenesis. Firstly, during the embryonic development stage, the PUM2 protein facilitates the transformation of embryonic stem cells into neural precursor cells, thereby promoting the development of neurons [14]. Secondly, during the neuronal differentiation stage, the radial glial precursor cells (RPs), which are the precursors of various types of neurons and glial cells in the central nervous system, can directly or indirectly promote the proliferation of intermediate progenitor cells, thereby differentiating into new neurons. The newly formed neurons then migrate to the basal layer of the cortex, forming the new cortical layer. Based on their differentiation sequence, they further construct the deep and shallow layers of the cortex [15]. In this process, the PUM2 protein can bind to the 4E transporter (4E-T) and co-bind to the neural stem cell-specific genes Brn1 and Tle4 mRNA, thereby affecting the translation of these two genes. When *PUM2* was knocked down, the Tle4 protein level in Brn1 positive neurons was significantly increased, especially in cortical neurons, causing abnormal co-expression of different

neuron-specific proteins. Therefore, in neural development, the PUM2 protein inhibits the production of specific proteins in different regions and neurons to ensure the temporal and spatial specificity of protein production in various subneurons, thereby preventing the abnormal co-expression of specific proteins between different cortical neurons [16]. Furthermore, the PUM2 protein can also form an RNA complex with the RNA-binding protein Staufen2 (Stau2). By directly regulating the subcellular localization and potential expression levels of target mRNAs in mammalian neural stem cells, it plays a regulatory role in the self-maintenance and differentiation processes of stem cells [17]. When *PUM2* and *STAU2* are functionally knocked down, the complex is disrupted, causing the radial glial progenitor cells to differentiate into neurons prematurely, leading to incorrect localization and expression of their target mRNAs. These results suggest that the PUM2 protein plays a stable and protective role in the normal differentiation and localization of neural cells.

PUM2 orchestrates neural development and migration precision

PUM2 protein further specifies neuronal identity determinants critical for subtype differentiation. The neocortex is the largest and most complex structure in the mammalian brain. It is located at the top layer of the cerebral hemispheres and is about 2–4 mm thick. It is divided into four planar regions and six spatial levels and plays a crucial role in processing sensory information, controlling movement, and advanced cognition [18]. Functionally distinct regions contain heterogeneous populations of neurons characterized by their morphology, connectivity, molecular code, and function. However, how do neurons in different regions connect, and how are subtypes distinguished? A study found that *Pum2* knockdown significantly increased the density of $SOX5^{+}$/$BCL11B^{+}$ neurons in the V layer of the anterior parietal and prefrontal cortex [19], In contrast, Rorβ+ neurons density in layer IV decreased under the same condition. To determine whether these alterations stemmed from changes in neuronal density, migration defects, or phenotypic reprogramming, the authors performed DAPI staining on layers IV and V in both *Pum2*-knockdown and control groups. Quantitative analysis revealed unchanged total neuronal counts in these layers, but significant shifts in neuronal subtype proportions. Therefore, the authors hypothesized that PUM2 protein did not affect the number of cells but caused changes in the neuron identity determinant on the surface of neurons. Collectively, these data establish *PUM2*'s essential role in specifying neuronal identity determinants during cortical development.

PUM2 protein is also important for the maturation of neurons. PUM2 and PUM1 protein could work together to promote the division and differentiation of neural stem cells, which has been confirmed in some studies. In a pivotal study [3], neural stem cells (NSCs) with concomitant *Pum1/Pum2* double-knockout (dKO) were compared to wild-type (WT) controls. Primary neurospheres (>30 μm diameter) were quantified at day 7 post-culture, dKO NSPCs formed much fewer and much smaller primary neurospheres compared with controls cells, but they also had lower self-renewing division. These data demonstrate that PUM2 protein deficiency critically compromises NSC self-renewal and differentiation capacity. To isolate *Pum2*-specific functions, mature cortical neurons were transduced with a shRNA construct targeting *Pum2* (*shPum2*) using lentiviral vectors [20], after confirming that the lentivirus could specifically knock down *Pum2*, the researchers found that the surface area of the somatic cells with *Pum2* knockdown decreased, indicating that the reduction of PUM2 protein would impair neuronal development and maturation. Collectively, these studies establish that PUM2 orchestrates neuronal growth, maturation, and molecular identity specification. However, current evidence derives exclusively from *in vitro* and animal models, lacking validation in human-derived systems (e.g., iPSC-derived neurons or postmortem tissue). Moreover, the mechanistic underpinnings – particularly spatiotemporally resolved RNA-protein interactomes and downstream signaling flux – demand multimodal dissection integrating live-cell imaging, ribonomics, and functional validation.

PUM2 adjusts dendritic and axonal morphogenesis

In neurons, axonal development including growth, branching, target innervation, and functional maintenance critically depends on localized protein synthesis. This process initiates when neuronal mRNAs assemble with ribonucleoprotein particles (RNPs) to form transport-competent complexes. These mRNA-RNP complexes are then actively trafficked along microtubules to subcellular compartments such as axons or dendrites for spatiotemporally precise translation. PUM2 protein exhibits strict somatic enrichment in developing neurons, spatially restricting target mRNA localization through sequence-specific binding. By recognizing PBEs, PUM2 protein retains transcripts in the soma, thereby preventing their axonal transport and subsequent translation [3]. Among them, glycogen synthase kinase 3β (Gsk3β) and cell adhesion molecule (L1cam) are both target mRNAs of PUM2 protein [21], PUM2 protein recognizes both transcripts via its PUM-HD domain and represses their

translation during local protein synthesis in axons. Gsk3β is a serine/threonine kinase expressed in axons, which regulates axonal growth through phosphorylating various proteins. For example, it phosphorylates microtubule-associated proteins, leading to decreased stability of microtubules and inhibition of axon elongation [22]. Concurrently, Gsk3β regulates the activity of actin, causing disruption of the polymerization-depolymerization balance of actin, leading to inhibition of axon elongation. L1cam is a transmembrane glycoprotein that mediates contact-dependent signaling through physical interaction with Robo receptors. This ligand-receptor complex orchestrates neurite fasciculation by coordinating F-actin dynamics within growth cones, enabling precise guidance of both axonal and dendritic processes [23], *Pum2*-deficient neurons exhibited axonal growth and branching defects *in vivo*, and impaired axon regeneration *in vitro* [21]. Collectively, *in vivo* and vitro evidence establishes. PUM2 protein as a critical regulator of axonal growth, development, and repair. While current data indicate PUM2 protein modulates axonal protein synthesis through mRNA transport regulation, direct experimental verification via coordinated manipulation of PUM2 protein and its effector proteins remains lacking. Furthermore, although phenotypic studies demonstrate PUM2's roles in axonal morphogenesis and regeneration, the underlying spatiotemporal mechanisms require deeper mechanistic dissection.

Additionally, PUM2 protein also plays an important regulatory role in the growth and development of neuronal dendrites. It has also been reported that PUM2 protein is more abundant in dendrites than in axons, with prominent localization to dendritic spines. These PUM2 proteins can bind to eukaryotic initiation factor 1A (EIF1A) and eukaryotic initiation factor 4E (EIF4E) in dendrites [24]. During translation initiation, EIF1A can bind to the 40S ribosome during translation initiation, accelerating the ribosome's start codon recognition and promoting mRNA expression. EIF4E can bind to the 5′ cap structure of mRNA during translation and recruit the small subunit of the ribosome and other translation initiation factors to form a translation complex, by suppressing EIF1A and EIF4E within dendritic spines, PUM2 protein regulates dendritic morphogenesis through localized translational control [25]. PUM2 protein can reduce dendritic spines and increase dendritic arborization in mature neurons, and increase dendritic spines and dendritic arborization in immature neurons [26]. Another study also showed that the knockout of the *Pum2* gene could lead to an increase in the number of short dendrites in mature hippocampus neurons [27]. The increased dendritic branching of hippocampal neurons resulting from PUM2 deficiency has also been confirmed in *Pum2*$^{-/-}$ mice [28], pyramidal cells in the CA1 layer of the hippocampus showed a significant increase in primary dendritic branches and a marked increase in synaptic density at the tips of their dendrites in *Pum2*$^{-/-}$ mice Furthermore, the length and width of the postsynaptic density projection were higher than those of WT mice. While PUM2 protein exhibits distinct, stage-specific functions in mature vs. immature neurons, the above findings from cellular and *in vivo* models have proposed its bidirectional regulatory role in dendritic morphogenesis. However, the molecular determinants underlying this context-dependent duality – particularly the temporal switch in RNA-binding specificity and downstream signaling cascades – remain incompletely characterized. Elucidating how PUM2's regulatory logic adapts across neurodevelopmental epochs represents a critical knowledge gap.

PUM2 modulates neural excitability

Neural conduction is an electrical and chemical sequence of events that occurs along nerve fibres and plays an important role in transmitting information, coordinating body movements, responding to external stimuli, and maintaining the function of the nervous system. However, neurons do not connect directly to each other, they communicate through synaptic structures. A complete synaptic structure includes the presynaptic membrane, the synaptic cleft, and the postsynaptic membrane, which are an asymmetric intercellular connection that can mediate rapid point-to-point communication between neurons, connect neurons to circuits, and process information during transmission [29]. PUM2 protein may be involved in the normal regulation of nerve signaling through the structure and function of synapses, the expression of sodium channels, and other aspects that influence the normal physiological function of the nervous system and the onset of disease.

PUM2 regulates synaptic excitability

Synapses are the key connection structures that enable information transmission between neurons and effector cells. Studies have shown that the PUM2 protein plays a significant role in regulating the formation of synapses, influencing the type, density, and maturation status of these structures. The deficiency of PUM2 results in a higher prevalence of asymmetric synapses and enhances synaptic transmission at excitatory synapses. It also increases both the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs), while reducing the amplitude of postsynaptic currents at inhibitory synapses. These changes collectively

lead to an overall increase in neuronal excitability [26, 28, 30]. In addition, the PUM2 protein also affects synapse function. First, PUM2 protein affects the levels of several key regulators of GABAergic neurotransmitters, such as porphyrins, vesicular inhibitory amino acid transporter protein (Vgat), sodium and chloride-dependent GABA transporter protein 1 (Gat1), glutamate decarboxylase 1 (Gad1) and somatostatin (SST), and subsequently affects the function of GABAergic synapses [31]. A proteomics study showed that these regulators associated with GABAergic synapses were reduced explicitly in neurons after *Pum2* knockout, and a reduction in the amplitude of small inhibitory postsynaptic currents (mPIPSCs) was detected in GABAergic neurons, but not in inhibitory presynaptic currents (IPSCs) or spontaneous postsynaptic currents [28]. Moreover, PUM2 protein enhances the expression of multiple excitatory synaptic proteins, notably upregulating the AMPA receptor subunit GluA2 (formerly GLUR2) in temporal lobe circuits, thereby potentiating glutamatergic transmission and increasing regional neuronal excitability. PUM2 protein can also modulate the concentration of acetylcholine in the synaptic cleft by affecting acetylcholinesterase (AChE), which in turn affects synaptic function. Previous studies have demonstrated that PUM2 protein specifically recognizes and binds to the 3′ untranslated region (3′-UTR) of AChE mRNA, thereby suppressing its translational activity. This post-transcriptional regulation leads to a significant reduction in acetylcholinesterase abundance within the synaptic cleft, ultimately impairing cholinergic neurotransmission by disrupting the physiological degradation of acetylcholine at synaptic junctions [32]. These findings demonstrate that PUM2 protein can influence synaptic excitability by affecting synapse types, synaptic regulators and the levels of pre- and postsynaptic currents.

PUM2 affects the expression of voltage-gated sodium channel proteins, leading to epilepsy susceptibility

Voltage-gated sodium channels are heteromeric transmembrane glycoprotein complexes localized on plasma membranes, comprising pore-forming α subunits and regulatory β subunits. These macromolecular assemblies serve as fundamental molecular determinants for the rapid initiation and propagation of action potentials through voltage-dependent conformational changes, thereby establishing essential electrochemical gradients that govern neuronal excitability and signal transduction in excitable tissues. The genes encoding sodium channels are evolutionarily highly conserved, and the α-subunit (Nav) family in the human genome comprises 10 genes, of which the genes SCN1A, SCN2A, and SCN8A encoding Nav1.1, Nav1.2, and Nav1.6 are highly expressed in neurons in the CNS [33]. The PUM2 protein could regulate the density of sodium channels by binding to the mRNA transcripts of SCN1A, SCN2A, and SCN8A, thereby inhibiting the normal translation processes of Nav1.1, Nav1.2, and Nav1.6 [34]. In the CNS, voltage-gated sodium channels are involved in the firing processes of neurons, and their abnormal expression is often the cause of epilepsy [35]. Nav1.1, encoded by SCN1A, is mainly distributed in GABAergic neurons in the nervous system, and its expression is closely related to the activity of GABAergic neurons. Abnormal expression of it will interfere with the activity of GABAergic neurons, affecting the balance of excitation and inhibition in the nervous system, and thus leading to epilepsy [36]. Nav1.2, encoded by SCN2A, is mainly located in excitatory neurons in the nervous system, and its expression level is related to the maturation and distribution of GABAergic neurons, playing an important role in the function of inhibitory neuronal networks [37]. Nav1.6, encoded by SCN8A, is mainly located at the excitatory axon terminals. An increase in its expression will cause excitatory neurons to be more prone to generating action potentials and increase the discharge frequency, which disrupts the balance of excitation and inhibition in the brain and leads to excessive excitation of neurons [38]. Experimental investigations demonstrated that *Pum2*-deficient mice exhibit a heightened susceptibility to spontaneous paroxysmal epileptiform activity. Mechanistic analyses through quantitative immunohistochemical analyses of hippocampal dorsal coronal sections (CA1 stratum pyramidale) revealed dysregulated sodium channel homeostasis, characterized by upregulated Nav1.1 (SCN1A) and Nav1.2 (SCN2A) isoforms juxtaposed with diminished Nav1.6 (SCN8A) expression. These alterations in voltage-gated sodium channel subtypes suggest a pathophysiological mechanism by which PUM2-mediated post-transcriptional regulation modulates neuronal hyperexcitability through coordinated regulation of Nav subunit stoichiometry in the nervous system [39].

PUM2 deficiency is associated with epilepsy

Epilepsy is a common neurological disorder that affects people worldwide, characterised by clinical features of

excessive and hypersynchronous neuronal discharges in the brain network. Under normal circumstances, the discharges between neurons are orderly and coordinated. However, in epilepsy patients, due to the disruption of the stability of the neuronal membrane, neurons become overly excited and generate abnormal electrical signals, which eventually trigger epileptic seizures [40]. Various underlying etiologies, including genetic susceptibility, structural abnormalities, metabolic disorders, and acquired brain injuries, cause this episodic disorder. Abnormal ion channel function is also an important factor in the pathogenesis of epilepsy. Ion channels are crucial regulators of the ion balance inside and outside neurons and play a key role in neuronal excitation and inhibition [41]. Some gene mutations or drug-induced ion channel abnormalities may lead to excessive neuronal excitation in the brain, thereby triggering epileptic seizures. Such abnormalities may include excessive opening or insufficient closure of ion channels, resulting in an imbalance of ion concentrations within neurons. As a chronic neurological disorder with severe comorbidities, epilepsy imposes a heavy burden on the public health system. It affects individuals and their families, including direct medical costs, social and psychological consequences, and an increased risk of death.

PUM2 is expressed in various regions of the cerebral cortex, amygdala, thalamus, hypothalamus and cerebellum, with the highest expression in the temporal lobe, and immunohistochemical staining of temporal cortex samples from patients with temporal lobe refractory epilepsy revealed significantly lower levels of PUM2 protein [30]. Further animal studies have also confirmed that *Pum2* deficiency results in spontaneous EEG abnormalities and lower seizure thresholds in mice [39]. The possible mechanisms are as follows: first, the expression of hundreds of mRNAs in the brain is upregulated in *Pum2* deficiency, and some of them are involved in the regulation of synaptic structure and excitability. In addition, PUM2 protein could regulate the expression levels of Nav1.1, Nav1.2, and Nav1.6 in the nervous system, where these sodium ion channels play an important role in epileptic seizures [42, 43]. As mentioned in the above content, the expression changes of these three sodium ion channels will affect the balance of excitation and inhibition in the brain, leading to excessive excitability of the nervous system and thus causing epilepsy. PUM2 protein has also been demonstrated to regulate several proteins associated with excitatory synaptic function, including GluA2. A reduction in PUM2 protein has been observed to increase GluA2 expression and neuronal excitation [28]. Consequently, the utilization of PUM2 protein as a therapeutic target to modulate sodium channel protein and neurotransmitter expression may prove efficacious in the amelioration of abnormal neuronal firing, thus providing a novel approach to the treatment of epilepsy.

PUM2 participates in neuronal injury after stroke

Stroke is the second leading cause of death and the third leading cause of disability globally. Its subtypes are distributed as follows: 62 % are ischemic strokes, 28 % are hemorrhagic strokes, and 10 % are subarachnoid haemorrhages. Both ischemic and hemorrhagic strokes can inflict damage on brain tissue, yet the mechanisms underlying the brain injury they trigger are distinct. In ischemic stroke, the primary causes of brain tissue damage encompass energy supply disruptions, excitotoxicity, oxidative stress, and inflammatory responses. For hemorrhagic stroke, the main mechanisms involve the space-occupying effect of the hematoma, the toxic effects of blood components, cerebral oedema, and elevated intracranial pressure. Moreover, regardless of whether an ischemic or hemorrhagic stroke occurs, it activates the immune system. This prompts peripheral immune cells to migrate to the perivascular space and brain parenchyma. These immune cells that infiltrate the brain release a substantial amount of proteases, reactive oxygen and nitrogen species, and inflammatory cytokines. This subsequently leads to nerve damage, thereby exacerbating neuroinflammation and neurovascular damage [44]. Consequently, regulating the levels of the inflammatory response and oxidative stress significantly influences the reduction of nerve damage and subsequent recovery. However, the PUM2 protein plays different regulatory roles in these two types of strokes.

Some animal and *in vitro* studies have shown that cerebral ischemia or hypoxia-glucose deprivation can lead to increased expression of PUM2. Further research has shown that high levels of PUM2 protein exacerbate I/R-induced neuroinflammation and brain damage. Sirtuin type 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylase, a member of the sirtuin family, which is closely associated with cell proliferation, differentiation, senescence, apoptosis, and metabolism. When ischemia-reperfusion occurs, SIRT1 is highly expressed to help restore mitochondrial homeostasis, regulate oxidative stress and inflammatory responses, and inhibit neuronal apoptosis, thereby protecting brain tissue from I/R injury. PUM2 protein could reduce the stability of SIRT1 and decrease its expression, leading to a decrease in the expression of SLC7A11, an increase in ferroptosis and neuroinflammation,

and an exacerbation of cerebral ischemia/reperfusion injury [45]. However, one study found that PUM2 protein was significantly lower in the early stages of subarachnoid hemorrhage animal models compared to controls, but increased in the later stages and that overexpression of PUM2 protein can reduce oxidative stress and neuronal death, thereby improving behavior and cognitive function in SAH animal models [46]. These results indicate that PUM2 protein plays a regulatory role in the prognosis of stroke and neuronal apoptosis. However, the role of the PUM2 protein in ischemic stroke and hemorrhagic stroke is opposite. This may be due to the different pathogenesis of these two diseases and the different pathways of oxidative stress and inflammatory responses they trigger, so their role may be different or even opposite.

PUM2 May inhibit vasculogenic mimicry of glioma

Glioma is the most common primary tumour in the brain and spinal cord. From a histological perspective, they can originate from normal glial cells, glial precursor cells, stem cells, and other cell types. Gliomas mainly include astrocytoma, oligodendroglioma, oligoastrocytoma, ependymoma, and neuronal and mixed neuronal-glial tumours. According to their degree of malignancy, they can be further classified into grade I pilocytic astrocytoma, pleomorphic xanthoastrocytoma and subependymal giant cell astrocytoma, grade II oligodendroglioma and astrocytoma, grade III anaplastic oligodendroglioma, anaplastic astrocytoma, anaplastic oligoastrocytoma, anaplastic ependymoma, and grade IV glioblastoma (GBM) [47]. The symptoms of glioma are diverse and vary depending on the site of origin, which can manifest as focal neurological deficits, encephalopathy or seizures. The aetiology and pathogenesis of glioma remain unclear, but high-dose ionising radiation and high-index gene mutations associated with rare syndromes are important risk factors. More than half of gliomas are glioblastomas. The average survival time of patients is about 15 months, and the 5-year survival rate is less than 7 % [48].

Vasculogenic mimicry (VM) is an endothelium-independent tumor microcirculation pattern manifested by tumor cells with “endothelial cell function” through their deformation and stromal remodeling to form pipeline structures, with erythrocytes visible inside the pipeline, capable of providing sufficient blood supply for tumor growth, and is closely related to tumor grading, invasion, metastasis, and poor prognosis [49]. Recent work identifies SUMOylation of PUM2 protein as the critical initiator of the PUM2-CEBPD-DSG2 axis, driving VM in gliomas [50]. Elevated expression of ubiquitin-conjugating enzyme E2I (UBE2I) during gliomagenesis promotes PUM2 protein SUMOylation in tumor tissues and cell. SUMOylation of PUM2 protein not only reduces the stability of the PUM2 protein but also weakens the inhibitory effect of PUM2 protein on CCAAT enhancer-binding protein δ (CEBPD) mRNA, thereby increasing CEBPD expression. CEBPD is a b-ZIP transcription factor that can bind to the DNA regulatory region to promote transcription, and the upregulated CEBPD facilitates binding to the upstream promoter region of the calcium-dependent desmosomal cadherin (DSG2) gene and upregulates DSG2 expression, which induces VM development in glioma. The abnormal expression of heme oxygenase-1 (HO-1) is closely related to the occurrence or progression of various tumours, including bladder cancer, breast cancer, colon cancer and glioma [51]. Analysis of the GSE4412 microarray dataset revealed an inverse correlation between *PUM2* and *HO-1* expression in grade IV gliomas. Complementary *in vitro* cellular assays demonstrated that HO-1 promotes proliferative clonality in glioma cell lines (A172 and U87-MG) [52]. However, this study did not extend to functional validation of PUM2 protein across glioma grades or elucidate its mechanistic role in tumour progression. We propose that this apparent contradiction is resolved by disease stage specificity: PUM2 protein degradation promotes VM in advanced tumour, while PUM2 protein suppression enables HO-1-driven proliferation in glioblastoma. Critically, neither study mechanistically links HO-1 to PUM2 protein SUMOylation or tests functional crosstalk between the VM and proliferation pathways. However, the findings on the role of PUM2 protein in the proliferation of gliomas are not consistent. Recent studies have shown that the expression of *PUM2* is increased in glioblastoma tumor tissue and cell lines. It has been shown to promote glioblastoma proliferation and migration by inhibiting the expression of the cell cycle regulator BTG1. Using shRNA to reduce the expression of the PUM2 protein can significantly inhibit the proliferation of glioblastoma cells while suppressing cell migration and invasion [53]. The opposing roles of PUM2 in glioma may be due to the experimental methods and cell types adopted in the research. The previous study selected human glioma tissues and human glioma cell lines (U251, U373) as research materials, and used a three-dimensional culture method to observe their angiogenesis simulation ability. The approach could more realistically reflect the growth characteristics of tumors in the human body. In contrast, the latter study maintained glioblastoma cell lines (U-87MG, T98G, U-251MG, and A172) in monolayer culture under standard adherent conditions, which possibly ignoring the potential influence

of PUM2 protein on angiogenesis simulation. The definitive mechanisms by which PUM2 regulates glioma proliferation and metastatic potential require further elucidation through advanced *in vivo* models and patient-derived organoid studies.

Conclusions

As an RNA-binding protein, PUM2 protein is highly expressed in the nervous system, where it plays a pivotal role in neuronal development and electrical signaling. PUM2 protein regulates these processes by binding to and inhibiting the translation of hundreds to thousands of target mRNAs, thereby maintaining the normal physiological functions of the nervous system. However, dysregulation of *PUM2* expression has been implicated in increasing susceptibility to or exacerbating the severity of various neurological disorders, including epilepsy, stroke, and glioma. Therefore, the development of drugs targeting PUM2 is of great significance in the treatment of specific neurological disorders. However, like other RBPs, the research on PUM2 protein as a therapeutic strategy for diseases is still in its infancy and progressing relatively slowly. This is because they play a pivotal role in the gene regulatory network, making it extremely difficult to predict the downstream effects of RNA-binding protein therapies. Some studies have used materials such as polyethyleneimine (PEI), glutathione (GSH), and mesoporous silica nanoparticles (MSN) to encapsulate anti-*Pum2* siRNA to form nanoparticles [54], in animal models, the expression of *Pum2* is intervened through intravenous injection to treat colorectal cancer. However, enabling the drug to pass through the physiological barriers in the body and accurately reach the designated site of action, as well as achieve precise targeted treatment of diseases and reduce side effects, remains a major challenge, further in-depth studies into the molecular mechanisms of PUM2 protein in these contexts are essential.

Funding information: This work was supported by the National Natural Science Foundation of China (82160320), the Central Government Guides Local Science and Technology Development Fund Projects (2021ZY0010), Science and Technology Programof the Joint Fund of Scientific Research for the Public Hospitals of Inner Mongolia Acadcmy of Medical Sciences (2023GLLH0309).

Author contribution: The idea for this review topic was conceived by JJZ and XB, who also contributed to revising the manuscript. CYL was responsible for designing and drafting the manuscript and figures. YG, MSZ, RRC, LJL, and TSZ took part in the article writing discussion and were involved in drafting and modifying the figure. All authors made contributions to revising the manuscript and approved the submitted version.

Conflict of interest: No conflicts of interest.

Data Availability Statement: Not applicable.

References

1. D'Amico D, Mottis A, Potenza F, Sorrentino V, Li H, Romani M, et al. The RNA-binding protein PUM2 impairs mitochondrial dynamics and mitophagy during aging. Mol Cell 2019;73:775–87.e10.
2. Lu G, Hall TM. Alternate modes of cognate RNA recognition by human PUMILIO proteins. Structure 2011;19:361–7.
3. Zhang M, Chen D, Xia J, Han W, Cui X, Neuenkirchen N, et al. Post-transcriptional regulation of mouse neurogenesis by Pumilio proteins. Genes Dev 2017;31:1354–69.
4. Zhao Y, Ma S, Liang L, Cao S, Fan Z, He D, et al. Gut microbiota-metabolite-brain axis reconstitution reverses sevoflurane-induced social and synaptic deficits in neonatal mice. Research 2024;7:0482.
5. Edwards TA. Bespoke RNA recognition by Pumilios. Biochem Soc Trans 2015;43:801–6.
6. Rösner L, Reichert D, Rau K, Muthmann N, Rentmeister A. Sequence-specific targeting of RNA. Methods 2022;205:73–82.
7. White EK, Moore-Jarrett T, Ruley HE. PUM2, a novel murine puf protein, and its consensus RNA-binding site. RNA 2001;7:1855–66.
8. Goldstrohm AC, Hall TMT, McKenney KM. Post-transcriptional regulatory functions of mammalian Pumilio proteins. Trends Genet 2018;34:972–90.
9. Bohn JA, Van Etten JL, Schagat TL, Bowman BM, McEachin RC, Freddolino L, et al. Identification of diverse target RNAs that are functionally regulated by human Pumilio proteins. Nucleic Acids Res 2018;46:362–86.
10. Van Etten J, Schagat TL, Hrit J, Weidmann CA, Brumbaugh J, Coon JJ, et al. Human Pumilio proteins recruit multiple deadenylases to efficiently repress messenger RNAs. J Biol Chem 2012;287:36370–83.
11. Sternburg EL, Karginov FV. Global approaches in studying RNA-binding protein interaction networks. Trends Biochem Sci 2020;45:593–603.
12. Spassov DS, Jurecic R. Mouse Pum1 and Pum2 genes, members of the Pumilio family of RNA-binding proteins, show differential expression in fetal and adult hematopoietic stem cells and progenitors. Blood Cells Mol Dis 2003;30:55–69.
13. Borsani E, Della Vedova AM, Rezzani R, Rodella LF, Cristini C. Correlation between human nervous system development and acquisition of fetal skills: an overview. Brain Dev 2019;41:225–33.
14. Wang J, Zhang T, Yu Z, Tan WT, Wen M, Shen Y, et al. Genome-wide RNA structure changes during human neurogenesis modulate gene regulatory networks. Mol Cell 2021;81:4942–53.e8.
15. Zeng B, Liu Z, Lu Y, Zhong S, Qin S, Huang L, et al. The single-cell and spatial transcriptional landscape of human gastrulation and early brain development. Cell Stem Cell 2023;30:851–66.e7.
16. Zahr SK, Yang G, Kazan H, Borrett MJ, Yuzwa SA, Voronova A, et al. A translational repression complex in developing mammalian neural stem cells that regulates neuronal specification. Neuron 2018;97:520–37.e6.
17. Vessey JP, Amadei G, Burns SE, Kiebler MA, Kaplan DR, Miller FD. An asymmetrically localized Staufen2-dependent RNA complex regulates

maintenance of mammalian neural stem cells. Cell Stem Cell 2012;11: 517–28.
18. Xing L, Wilsch-Bräuninger M, Huttner WB. How neural stem cells contribute to neocortex development. Biochem Soc Trans 2021;49: 1997–2006.
19. Harb K, Richter M, Neelagandan N, Magrinelli E, Harfoush H, Kuechler K, et al. Pum2 and TDP-43 refine area-specific cytoarchitecture post-mitotically and modulate translation of Sox5, Bcl11b, and Rorb mRNAs in developing mouse neocortex. eLife 2022;11: e55199.
20. Schieweck R, Schöneweiss EC, Harner M, Rieger D, Illig C, Saccà B, et al. Pumilio2 promotes growth of mature neurons. Int J Mol Sci 2021;22: 8998.
21. Martínez JC, Randolph LK, Iascone DM, Pernice HF, Polleux F, Hengst U. Pum2 shapes the transcriptome in developing axons through retention of target mRNAs in the cell body. Neuron 2019;104:931–46.e5.
22. Liz MA, Mar FM, Santos TE, Pimentel HI, Marques AM, Morgado MM, et al. Neuronal deletion of GSK3β increases microtubule speed in the growth cone and enhances axon regeneration via CRMP-2 and independently of MAP1B and CLASP2. BMC Biol 2014;12:47.
23. Chen CH, Hsu HW, Chang YH, Pan CL. Adhesive L1CAM-Robo signaling aligns growth cone F-actin dynamics to promote axon-dendrite fasciculation in C. elegans. Dev Cell 2019;48:215–28.e5.
24. Vessey JP, Vaccani A, Xie Y, Dahm R, Karra D, Kiebler MA, et al. Dendritic localization of the translational repressor Pumilio 2 and its contribution to dendritic stress granules. J Neurosci 2006;26:6496–508.
25. Moon IS, Cho SJ, Seog DH, Walikonis R. Neuronal activation increases the density of eukaryotic translation initiation factor 4E mRNA clusters in dendrites of cultured hippocampal neurons. Exp Mol Med 2009;41: 601–10.
26. Vessey JP, Schoderboeck L, Gingl E, Luzi E, Riefler J, Di Leva F, et al. Mammalian Pumilio 2 regulates dendrite morphogenesis and synaptic function. Proc Natl Acad Sci USA 2010;107:3222–7.
27. Randolph LK, Pauers MM, Martínez JC, Sibener LJ, Zrzavy MA, Sharif NA, et al. Regulation of synapse density by Pumilio RNA-binding proteins. Cell Rep 2024;43:114747.
28. Dong H, Zhu M, Meng L, Ding Y, Yang D, Zhang S, et al. Pumilio2 regulates synaptic plasticity via translational repression of synaptic receptors in mice. Oncotarget 2018;9:32134–48.
29. Südhof TC. The cell biology of synapse formation. J Cell Biol 2021;220: e202103052.
30. Wu XL, Huang H, Huang YY, Yuan JX, Zhou X, Chen YM. Reduced Pumilio-2 expression in patients with temporal lobe epilepsy and in the lithium-pilocarpine induced epilepsy rat model. Epilepsy Behav 2015; 50:31–9.
31. Schieweck R, Riedemann T, Forné I, Harner M, Bauer KE, Rieger D, et al. Pumilio2 and Staufen2 selectively balance the synaptic proteome. Cell Rep 2021;35:109279.
32. Marrero E, Rossi SG, Darr A, Tsoulfas P, Rotundo RL. Translational regulation of acetylcholinesterase by the RNA-binding protein Pumilio-2 at the neuromuscular synapse. J Biol Chem 2011;286:36492–9.
33. Meisler MH, Hill SF, Yu W. Sodium channelopathies in neurodevelopmental disorders. Nat Rev Neurosci 2021;22:152–66.
34. Lin WH, Baines RA. Regulation of membrane excitability: a convergence on voltage-gated sodium conductance. Mol Neurobiol 2015;51:57–67.
35. Fan X, Huang J, Jin X, Yan N. Cryo-EM structure of human voltage-gated sodium channel Na(v)1.6. Proc Natl Acad Sci U S A 2023;120: e2220578120.
36. Escayg A, Goldin AL. Sodium channel SCN1A and epilepsy: mutations and mechanisms. Epilepsia 2010;51:1650–8.
37. Zhao T, Chen F, Wang L, Xie Y, Yang M, Feng F. SCN2A gene mutations with epilepsy: single center experience. Ital J Pediatr 2025;51:170.
38. Meisler MH. SCN8A encephalopathy: mechanisms and models. Epilepsia 2019;60(3 Suppl):S86–s91.
39. Follwaczny P, Schieweck R, Riedemann T, Demleitner A, Straub T, Klemm AH, et al. Pumilio2-deficient mice show a predisposition for epilepsy. Dis Model Mech 2017;10:1333–42.
40. Ali A. Global health: Epilepsy. Semin Neurol 2018;38:191–9.
41. Oyrer J, Maljevic S, Scheffer IE, Berkovic SF, Petrou S, Reid CA. Ion channels in genetic epilepsy: from genes and mechanisms to disease-targeted therapies. Pharmacol Rev 2018;70:142–73.
42. Kaplan DI, Isom LL, Petrou S. Role of sodium channels in epilepsy. Cold Spring Harb Perspect Med 2016;6:a022814.
43. Driscoll HE, Muraro NI, He M, Baines RA. Pumilio-2 regulates translation of Nav1.6 to mediate homeostasis of membrane excitability. J Neurosci 2013;33:9644–54.
44. Brea D. Post-stroke immunosuppression: exploring potential implications beyond infections. Eur J Neurosci 2023;58:4269–81.
45. Liu Q, Liu Y, Li Y, Hong Z, Li S, Liu C. PUM2 aggravates the neuroinflammation and brain damage induced by ischemia-reperfusion through the SLC7A11-dependent inhibition of ferroptosis via suppressing the SIRT1. Mol Cell Biochem 2023;478:609–20.
46. Gu J, Lu J, Yang J, Liu Y, Zhu X, Zhang J, et al. Norad competently binds with Pum2 to regulate neuronal apoptosis and play a neuroprotective role after SAH in mice. Neuroscience 2023;535:108–23.
47. Chen R, Smith-Cohn M, Cohen AL, Colman H. Glioma subclassifications and their clinical significance. Neurotherapeutics 2017;14:284–97.
48. Liang T, Gu L, Kang X, Li J, Song Y, Wang Y, et al. Programmed cell death disrupts inflammatory tumor microenvironment (TME) and promotes glioblastoma evolution. Cell Commun Signal 2024;22:333.
49. Luo Q, Wang J, Zhao W, Peng Z, Liu X, Li B, et al. Vasculogenic mimicry in carcinogenesis and clinical applications. J Hematol Oncol 2020;13:19.
50. Wang D, Ruan X, Liu X, Xue Y, Shao L, Yang C, et al. SUMOylation of PUM2 promotes the vasculogenic mimicry of glioma cells via regulating CEBPD. Clin Transl Med 2020;10:e168.
51. Hou C, Wan Q, Xiao L, Xiao Q, Zhang M, Yan N. Inhibition of heme oxygenase 1 suppresses growth, migration, and invasion, and regulates tumor-infiltrating CD8+ T cells and in uveal melanoma. Investig Ophthalmol Vis Sci 2024;65:37.
52. Castruccio Castracani C, Longhitano L, Distefano A, Di Rosa M, Pittalà V, Lupo G, et al. Heme Oxygenase-1 and carbon monoxide regulate growth and progression in glioblastoma cells. Mol Neurobiol 2020;57: 2436–46.
53. Wang Y, Sun W, Yang J, Yang L, Li C, Liu H, et al. PUM2 promotes glioblastoma cell proliferation and migration via repressing BTG1 expression. Cell Struct Funct 2019;44:29–39.
54. Gong Y, Liu Z, Yuan Y, Yang Z, Zhang J, Lu Q, et al. PUMILIO proteins promote colorectal cancer growth via suppressing p21. Nat Commun 2022;13:1627.