

Research Progress on PATJ and Underlying Mechanisms Associated with Functional Outcomes After Stroke

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Abstract: Cell polarity is an intrinsic property of epithelial cells regulated by scaffold proteins. The CRB (crumbs) complex is known to play a predominant role in the dynamic cooperative network of polarity scaffold proteins. PATJ (PALS1-associated tight junction) is the core component in the CRB complex and has been highly conserved throughout evolution. PATJ is crucial to several important events in organisms' survival, including embryonic development, cell polarity, and barrier establishment. A recent study shows that PATJ plays an important role in functional outcomes of stroke. In this article, we elaborate on the biological structure and physiological functions of PATJ and explore the underlying mechanisms of *PATJ* genetic polymorphism that are associated with poor functional outcomes in ischemic stroke.

Keywords: PATJ, cell polarity, stroke

Introduction

Cell polarity is known to be essential for cellular functions,¹ especially in epithelial cells.² Research has shown that polarity protein complexes play an important role in the process of cell polarization³ and are involved in the formation of intercellular junction complexes. Cell polarity protein complexes mainly include the CRB (crumbs) - PALS1 (protein associated with LIN-7 1) -PATJ (PALS1-associated tight junction) complex, PAR3 (protease activated receptor 3) - PAR6 (protease activated receptor 6) - aPKC (atypical protein kinase C) complex at the top of the cell, and the SCRIB (scribble) - DLG (discs large) - LGL (lethal giant larvae) complex at the base (shown in Figure 1). These components cooperate with each other and participate in the establishment and stabilization of epithelial polarity.⁴ PATJ is an essential component of CRB complex. It is involved in a series of biological processes, such as cell migration, angiogenesis, and junction complex construction. It has also been found to be associated with tumorigenesis,⁵ viral infection⁶ and other diseases.

Ischemic stroke is the most common fatal disease in China, and the majority of survivors will remain permanently disabled. Recently, increasing number of studies have focused on the clinical outcomes after stroke. The functional prognosis of stroke patients is not only affected by disease severity and rehabilitation strategy, but also partly attributed to inflammatory responses, genetics, blood-brain-barrier (BBB) permeability, collateral circulation and other factors.⁷ Combined with

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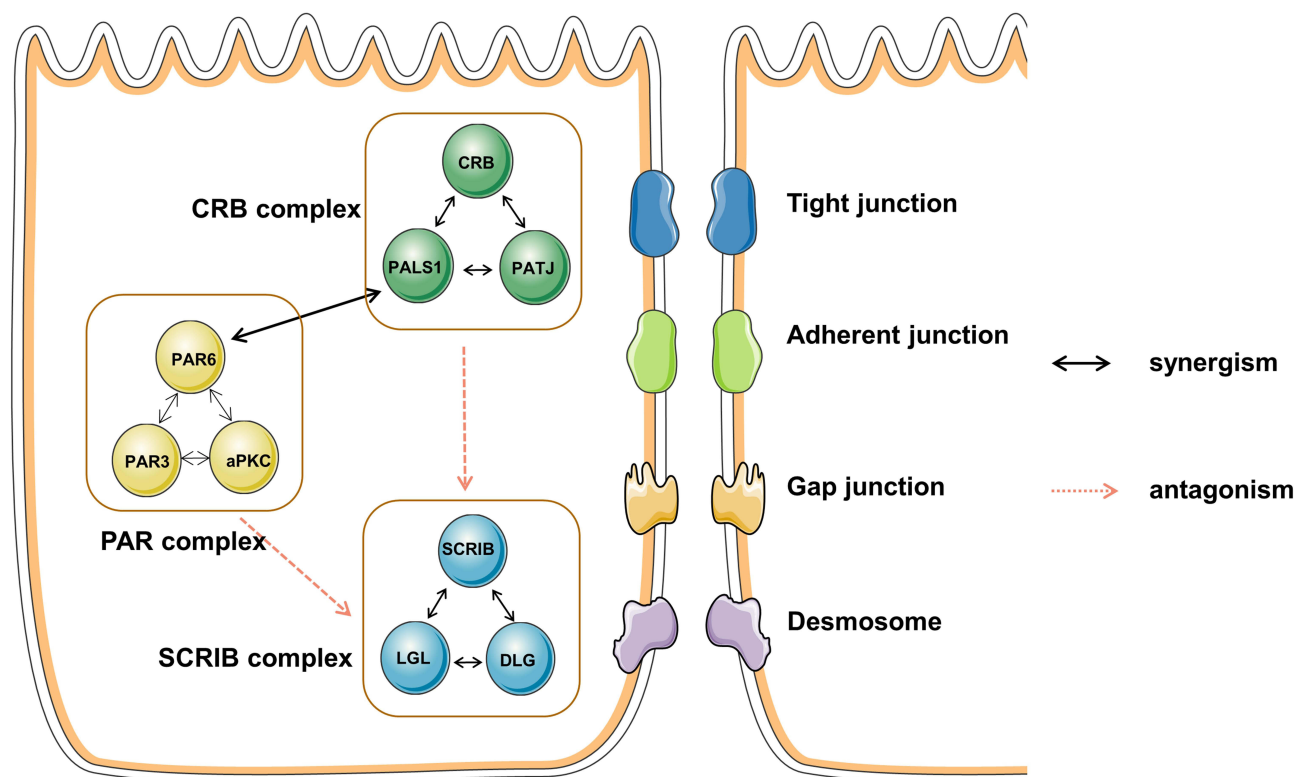


Figure 1 Dynamic cooperative network of polarity protein complex.

Abbreviations: CRB, crumb; PATJ, PALS1-associated tight junction; PALS1, protein associated with Lin-7 I; PAR6, protease activated receptor 6; PAR3, protease activated receptor 3; aPKC, atypical protein kinase C; SCRIB, scribble; LGL, lethal giant larvae; DLG, discs large.

physiological functions of PATJ, we hypothesized that PATJ may be an important predictor of stroke prognosis. This conjecture is supported by a largest genome-wide association study (GWAS) on ischemic stroke outcomes to date with 1225 stroke patients enrolled in 12 cohorts, in which Mola-Caminal and colleagues⁸ found that single nucleotide polymorphisms (SNPs) in *PATJ* were associated with poor prognosis at 3 months after a stroke. The top variant was rs76221407. This study was the first to demonstrate an association between *PATJ* and prognosis of ischemic stroke at a large-scale, suggesting that *PATJ* may be a new target for rehabilitation strategies after a stroke. However, the biological mechanism of PATJ in stroke is unknown. In this article, we briefly review the basic structure and physiological functions of PATJ and explore the potential mechanisms by which abnormal expression of PATJ may contribute to poor outcomes after stroke.

PATJ and Its Homologue

PATJ is a polar scaffold protein that interacts with other scaffold proteins (such as PALS1, CRB, etc.) through

domains of protein–protein interaction to form homologous or heterologous protein complexes, participating in the establishment of cell polarity and performing corresponding biological functions. PATJ is widely distributed in the brain and skeletal muscle, and is located in different regions of cells during the process of cell polarization. PATJ localizes to the vacuolar apical compartment (VAC) in nonpolarized cells, and targets the apical region and tight junctions (TJs) during polarization to participate in the formation of intercellular junction structures.

The story of discovery of PATJ is interesting. PATJ was originally known as hINADL (human InaD like), and was initially considered to be a homologue of INADL (inactivation no after-potential D) in *Drosophila*.⁹ hINADL was thought to contribute to clustering membrane proteins.¹⁰ However, after the analysis of PATJ domains, it was found that the PDZ (postsynaptic density-95/disc large/ZO-1) domains of PATJ showed strong similarity to those domains of DLT (discs-lost) in *Drosophila*. The homology was more than 50%. DLT, also known as DPATJ,¹¹ is a cytoplasmic PDZ domain protein in *Drosophila*, which consists of an L27 (lin2 lin7 binding) domain at the N-terminal and four

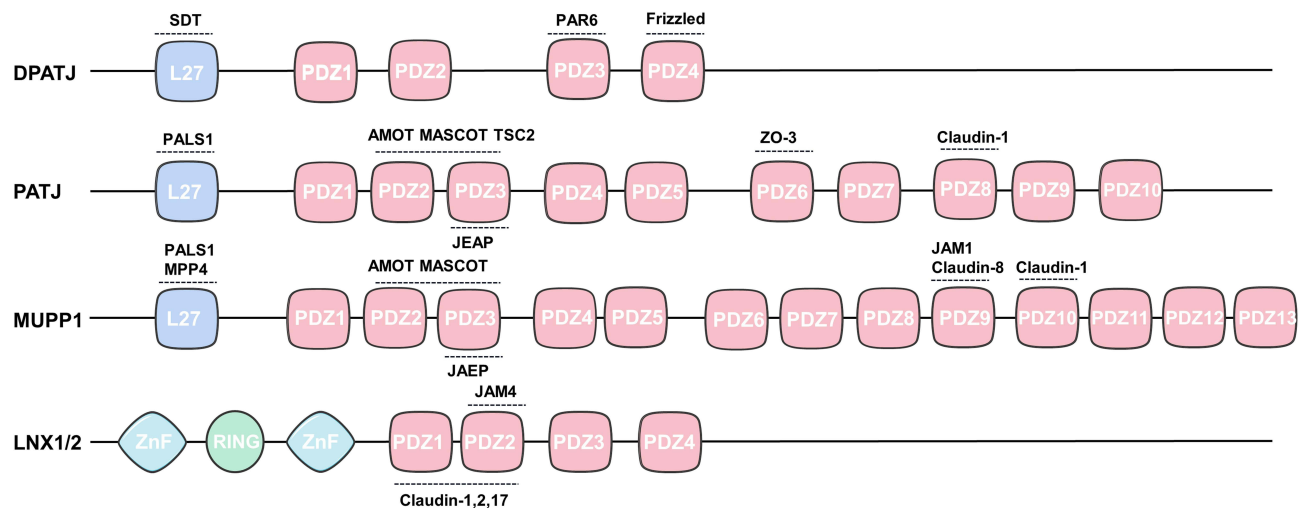


Figure 2 The structure of PATJ and its homologues.

Abbreviations: SDT, stardust; PAR6, protease activated receptor 6; PALS1, protein associated with LIN-7 I; PATJ, PALS1-associated tight junction; AMOT, angiomin; MASCOT, TMAGI-I-associated coiled-coil tight junction protein; TSC2, the tuberous sclerosis 2 protein; JEAP, junction-enriched and -associated protein; JAM1, junctional adhesion molecule 1; MUPP1, multiple PDZ domain protein 1; LNX1/2, liver of NUMB protein X1 and X2; L27, lin2 lin7 binding; PDZ, postsynaptic density-95/diss large/ ZO-1; ZnF, zinc finger motif; RING, really interesting new gene; JAM4, junctional adhesion molecule 4.

PDZ domains at the C-terminal. The two PDZ domains at the terminal are related to cell polarity¹² (shown in Figure 2). Considering that the biological structures of DPATJ and hINADL look similar, and that they are both involved in the establishment and maintenance of cell polarity, scientists renamed hINADL to PATJ, and deemed that PATJ was the homologue of DPATJ in mammals.

PATJ contains one L27 domain and ten PDZ domains^{13,14} (shown in Figure 2). Through the second and third PDZ domains, PATJ binds to the angiomin (AMOT) - binding protein family to establish tight junctions and stabilize epithelial polarity. PATJ can also use the second PDZ domain to interact with the tuberous sclerosis 2 protein (TSC2),¹⁵ thus linking the mammalian target of rapamycin (mTOR) pathway with the CRB complex and supporting the hypothesis that cell polarity proteins could participate in signal transduction. The carboxyl termini of Zona occludens-3 (ZO-3) and claudin-1 interact with the sixth and eighth PDZ domain, respectively, suggesting that PATJ plays an important role in the establishment of TJs. The association between ZO-3 and PATJ may be crucial for the recruitment of PATJ and related proteins to TJs. PATJ without the sixth PDZ domain was found to be incorrectly located in the region far from TJs, while the loss of the claudin-1 binding domain did not affect PATJ localization.¹²

Although we did not find relevant literatures about functions of PATJ in the pathological process of stroke, we noticed

that MUPP1 (multi-PDZ domain protein), a homologue of PATJ in humans, has been proven to be related to central nervous system diseases such as congenital hydrocephalus¹⁶ and autism.¹⁷ MUPP1 contains one L27 domain and thirteen PDZ domains (as shown in Figure 2). PDZ domains in MUPP1 can also be combined with PALS1 and the AMOT-related proteins is much lower than that for PATJ.^{12,18} MUPP1 can participate in the construction of intercellular junction complexes by binding to the transmembrane protein JAM1 (junctional adhesion molecule 1) and claudin-8.¹⁹ Given the similar structures and biological functions of MUPP1 and PATJ, we speculate that PATJ may also play a role in the occurrence and development of nervous system diseases.

Other than DPATJ and MUPP1, other proteins with multiple PDZ domains as main functional units, such as LNX1 (liver of NUMB protein X1) and LNX2 (liver of NUMB protein X2), are also considered to be homolog of PATJ (as shown in Figure 2). They take part in the process of nerve signal transduction²⁰ and tumorigenesis in the brain,²¹ further suggesting that PATJ may be involved in neurological disorders.

Underlying Mechanisms of Association Between PATJ and Stroke Outcomes

Ischemic stroke is a common disease in the world, characterized by high disability rate, high recurrence rate and high

mortality. Clinical prognosis is a core issue in stroke research, with significant implications on survival and quality-of-life. Common risk factors of poor functional outcomes post-stroke include advanced age, smoking, hypertension and hyperlipidemia, the *PATJ* gene polymorphism is also correlated with clinical outcomes at 3 months post-stroke. However, the mechanisms are still unclear. Based on published experiments and clinical evidence, we preliminarily discuss the potential mechanisms through which *PATJ* could cause poor prognosis after a stroke (shown in Figure 3).

PATJ Regulates Stroke Outcomes via Cell Polarization

Cell polarization—the asymmetric distribution of cytoskeleton, proteins, and organelles to specific regions in cells—plays an important role in physiological and pathological processes such as angiogenesis, and homeostasis.²² Epithelial cells use cell polarity to form a barrier against bacteria and viruses to ensure homeostasis. Asymmetric division of nerve cells, cell migration, axon formation and signal

transduction also depend on cell polarity.²³ Abnormal cell polarity is an important pathological mechanism in central nervous system diseases. For example, abnormal expression of the polarity scaffold-protein LGL leads to neuronal cell migration disorder, resulting in epileptic seizures.²⁴

It has been reported that the *dpaj* mutation in *Drosophila* could severely disrupt the apical localization of CRB, resulting in the loss of cell polarity.^{11,25,26} *PATJ* is the homologue of *DPATJ* in mammals, which has the similar structure and physiological functions to *DPATJ*. As such, it can also stabilize normal structure of polar protein complexes such as CRB and PAR complex,^{27,28} regulate the formation and maintenance of cell polarity, and participate in axon growth, angiogenesis, and cell migration. It follows that *PATJ* could potentially affect the functional prognosis of ischemic stroke through these pathways.

Axons are an essential part of signal transmission between neurons. Neuronal somas emit nerve impulses, which are transmitted through the axon to other neurons to carry out biological functions. Axons grow under the

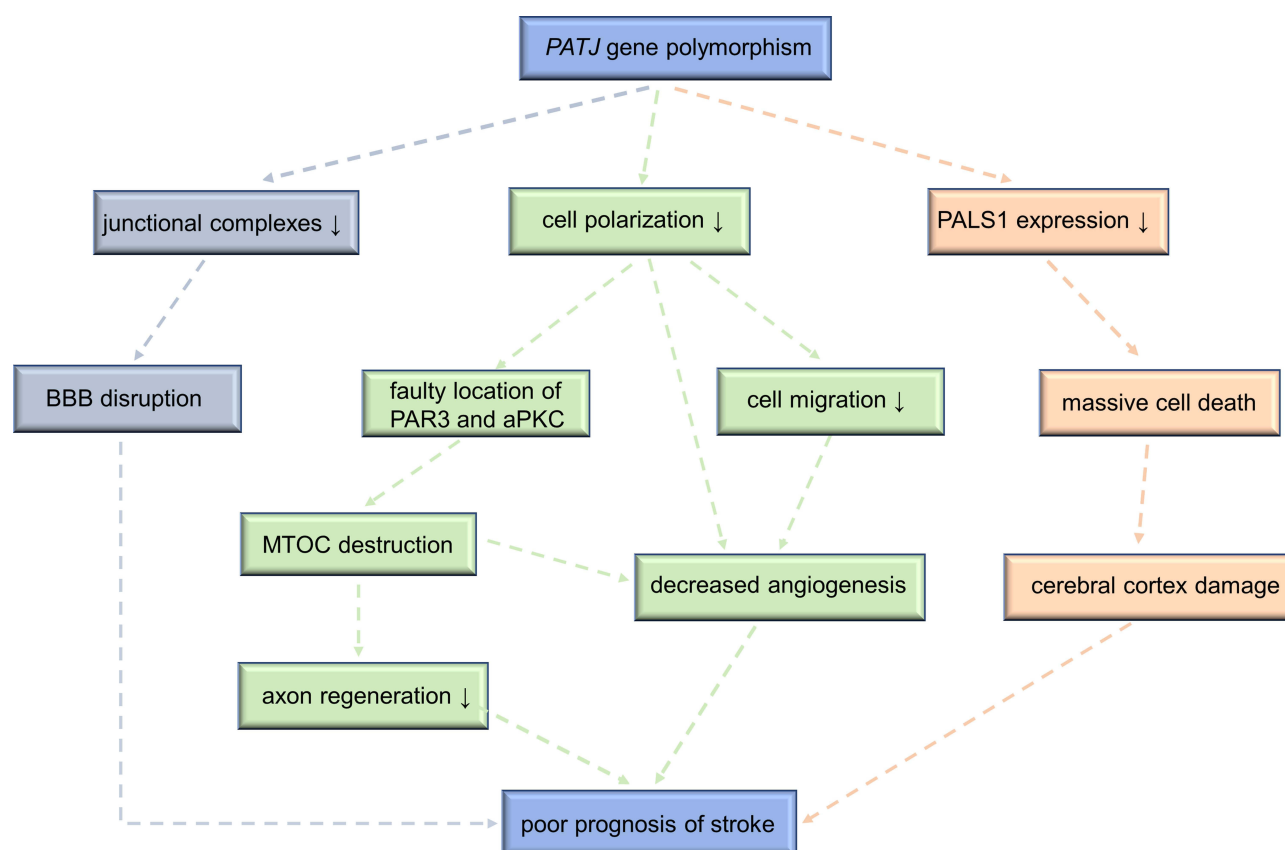


Figure 3 The underlying mechanisms that *PATJ* genetic mutations lead to poor prognosis of stroke.

Abbreviations: *PATJ*, PALS1-associated tight junction; PALS1, protein associated with Lin-7 I; PAR3, protease activated receptor 3; aPKC, atypical protein kinase C; BBB, blood-brain-barrier; MTOC, microtubule-organizing center.

control of cell polarity and form synapses with dendrites after reaching the designated location, thus ensuring the accuracy of neuronal connections, material transport and signal transduction.²⁹ Regeneration and repair of axons and dendrites are important for the functional recovery of the central nervous system.³⁰ Microtubule-organizing center (MTOC) is involved in the formation of neuronal axons and dendrites,³¹ and the correct assembly of microtubules in the growth cone is the basis of neurite growth and extension.³² Abnormal expression of the *PATJ* gene leads to the faulty localization of polarity scaffold-protein PAR3 and aPKC,³³ which affects the proper assembly of microtubule structure. This may explain why the *PATJ* gene polymorphism contributes to poor neurological recovery after a stroke. Although there are no basic experiments or clinical studies confirming that *PATJ* gene polymorphism is associated with axonal dysplasia, its homologues LNX1 and LNX2 have been shown to play an important role in synapse formation and signal transmission.²⁰ Further studies are needed to confirm the relationship between *PATJ* and axons and dendrites.

Angiogenesis is a protective mechanism after a stroke. Neovascularization can mitigate hypoperfusion in ischemic brain tissue by increasing the supply of oxygen and nutrients, thus saving neurons in the ischemic penumbra. Cell polarity, which requires the participation of *PATJ*, is a prerequisite for angiogenesis. Under the control of cell polarity, single cells gather around the lumen to form the vascular wall, with the top of cells facing the lumen. However, in the *PATJ* RNA-knockout cell model, epithelial cells were distributed in a disordered manner and no angiogenesis was observed. After reintroducing *PATJ* back to the *PATJ* RNAi cell, the polarity defect was reversed and cells gathered to form the single-lumen polarized vessel.³⁴ This suggests that *PATJ* plays a key role in angiogenesis by establishing and maintaining cell polarity.³⁵

Cell Migration is a Potential Mechanism Affecting Prognosis of Stroke

Cell migration, also known as cell crawling, refers to cell movement caused by signals or changes in the concentration gradient of a substance. Cell migration is a common movement mode of cells, which is an important part of organismal growth and development. Angiogenesis is not only regulated by cell polarity, but also related to cell migration. In the process of angiogenesis, angioblasts migrate to specific locations, differentiate into endothelial

cells, and then aggregate into cord-like structures composed of solid cell masses. After forming the vascular lumen, vascular cords form the primary vascular network.

PATJ mainly relies on MTOC to regulate cell migration. One of the characteristics of cell migration is the reorientation of MTOC to point in the correct direction of movement. In the *PATJ* knockout cell model, both PAR3 and aPKC in the PAR complex were not located at the leading edge of migrating cells, thus resulting in microtubule structure destruction and affecting the location of MTOC.^{33,36} Additionally, *PATJ* can regulate cell migration through binding to Ras homolog gene family member A (RhoA),³⁷ spaghetti squash (SQH),³⁸ kidney and brain expressed protein (KIBRA)³⁹ and other molecules.

Abnormal Expression of *PATJ* Affects the Formation of Junction Complexes

Cell polarity is crucial for the normal function of most cells. It is characterized by the establishment of cell axes that allows different proteins and lipids to be asymmetrically distributed to specific regions, and subsequently performing their functions. There are junctional complexes such as TJs and adherens junctions (AJs) between polarized epithelial cells, which form physical barriers separating the top and base of the cell. TJs line the top of AJs, forming physical barriers that block soluble molecules through the intercellular spaces. The AJs can maintain normal tissue structures by mechanically connecting adjacent cells. Junctional complexes are considered to be indispensable for BBB, and the permeability of BBB is related to functional prognosis of ischemic stroke. It is reported that BBB permeability is an independent predictor of ischemic stroke. Those with damaged BBB integrity have worse outcomes and poorer prognosis, independent of age, sex, infarct sizes and other factors.⁴⁰

PATJ takes part in the establishment and maintenance of junctional complexes. Overexpression or deletion of *PATJ* in epithelial cells will destroy the specific localization of tight junction proteins, including ZO-1, ZO-3 and occludin, in the lateral membrane of cells; as well as affect the distribution of the CRB complex, leading to failure of PALS1 and CRB3 to gather at the tight junction. It has been suggested that *PATJ* is involved in the construction of tight junctions by linking polarity-proteins on the apical and basolateral membranes in cells.^{41–43} In a cell model with abnormal *PATJ* expression, the transepithelial

resistance decreased significantly, reflecting the functional impairment of barrier formed by TJs. The downregulation of PALS1 was also observed.⁴⁴ Normal functions of TJs were not recovered after supplementing PALS1, indicating that PATJ is irreplaceable in the formation and normal functioning of TJs.

PATJ also supports the stability of the AJs by regulating myosin activity. PATJ binds to the subunit of myosin phosphatase and reduces its ability to dephosphorylate, resulting in myosin activation. In *PATJ*-mutated cells, myosin is located in incorrect regions, and AJs disintegrate.³⁸

Although there is no direct evidence that PATJ is related to the structures and functions of the BBB, there is evidence of such a relationship with MUPP1, which is thought to have similar physiological functions as PATJ. It is found that *MUPP1* gene knockout mice had poor BBB integrity,¹⁶ suggesting that normal *MUPP1* expression was the premise of maintaining BBB structures and functions.⁴⁵ *MUPP1* gene knockout also results in ependymocyte necrosis and astrocyte proliferation, leading to the stenosis of midbrain aqueduct and the obstruction of cerebrospinal fluid reflux.¹⁶ Hydrocephalus was induced in most mice and some died of cerebral hemorrhage. In this study, down-regulation of PALS1 levels and tight junction destruction were also observed.

Based on the theory that there are significant overlaps between the physiological functions of MUPP1 and PATJ, and that the relationship between PALS1, tight function and PATJ is closer than that with MUPP1,¹⁸ we infer that the *PATJ* gene polymorphism will damage the BBB due to cell junction destruction. This allows hyperactivated inflammatory substances to enter the brain, leading to an imbalance in central nervous system hemostasis and thus affecting post-stroke clinical outcomes. Abnormal *PATJ* expression can also cause hydrocephalus, cerebral hemorrhage and other adverse events, further contributing to the poor prognosis of stroke patients.

PALS1 Deficiency Links PATJ to Stroke Prognosis

PALS1 is necessary for the development of the cerebral cortex. PALS1 is associated with the number of γ -aminobutyric acid (GABA) transporters, mTOR signal transmission, and primary cilia length in the central nervous system,^{46,47} thereby participating in the transduction of survival signals and the development of the nervous system. Conditional removal of PALS1 causes excessive generation of early-born postmitotic neurons followed by

massive and rapid cell death, which destroys the structure of the cerebral cortex.^{4,46} Additionally, the levels of PATJ and PALS1 in cells are heavily influenced by one another. The integrity of the PATJ structure is key to the localization of PALS1 in the TJs.^{44,48} If the PATJ levels are low, PALS1 expression will be missing in the cell, while PATJ overexpression results in faulty localization of PALS1. Therefore, PATJ may indirectly affect nervous system development through regulating PALS1.

Conclusion

PATJ is an important cellular polar scaffold protein and is crucial for cell polarization, cell migration, and blood-brain-barrier formation among other functions. *PATJ* gene polymorphism may lead to poor functional outcomes in stroke patients through inhibiting axon regeneration and angiogenesis as well as destroying blood-brain-barrier integrity. Basic science experiments and clinical studies are needed to explore possible reasons why the *PATJ* gene polymorphism contributes to poor prognosis of stroke and determine whether it could be a potential target in stroke diagnosis and treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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