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REVIEW

Axon regeneration impediment: the role of paired immunoglobulin-like receptor B

Jing Liu[1,*], **Yan Wang**[1,2], **Wei Fu**[1,2]

1 Neonatal Intensive Care Center, BAYI Children's Hospital, Beijing Military General Hospital of Chinese PLA, Beijing, China
2 Graduate School, Southern Medical University, Guangzhou, Guangdong Province, China

***Correspondence to:**
Jing Liu, M.D., liujingbj@live.cn.

orcid:
0000-0001-8356-9515 (Jing Liu)

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Abstract

Regenerative capacity is weak after central nervous system injury because of the absence of an enhancing microenvironment and presence of an inhibitory microenvironment for neuronal and axonal repair. In addition to the Nogo receptor (NgR), the paired immunoglobulin-like receptor B (PirB) is a recently discovered coreceptor of Nogo, myelin-associated glycoprotein, and myelin oligodendrocyte glycoprotein. Concurrent blocking of NgR and PirB almost completely eliminates the inhibitory effect of myelin-associated inhibitory molecules on axonal regeneration. PirB participates in a key pathological process of the nervous system, specifically axonal regeneration inhibition. PirB is an inhibitory receptor similar to NgR, but their effects are not identical. This study summarizes the structure, distribution, relationship with common nervous system diseases, and known mechanisms of PirB, and concludes that PirB is also distributed in cells of the immune and hematopoietic systems. Further investigations are needed to determine if immunomodulation and blood cell migration involve inhibition of axonal regeneration.

Key Words: *nerve regeneration; brain injury; paired immunoglobulin-like receptor B; myelin inhibitory molecule; axons; regeneration; Rho-ROCK signaling pathway; NSFC grant; neural regeneration*

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Introduction

Compared with the peripheral nervous system, axons in the adult mammalian central nervous system cannot effectively regenerate after injury. In addition to the low intrinsic regenerative capacity of neurons, glial scar formation, and lack of growth-promoting factors, neural regeneration inhibiting factors activate diverse signal transduction cascades in different cell types, which inhibits axonal regeneration and may be the key to ineffective axonal regeneration (Rauschecker and Stratakis, 2012). Many signaling pathways (including Ras homolog gene/Rho-associated coiled coil-forming protein kinase (Rho-ROCK), Notch, MAPK, Wnt/β-catenin, mTOR, and ephephrin) participate in and affect repair or regeneration of neurons and axons in the central nervous system (Tatsumi et al., 2010). The cyclic adenosine monophosphate-protein kinase A (cAMP-PKA) and Rho-ROCK signaling pathways are key signal transduction pathways for regulating neural and axonal regeneration (Brown et al., 2012). Activating the cAMP-PKA signal transduction pathway or inhibiting the Rho-ROCK signal transduction pathway promotes neural and axonal regeneration (Brown et al., 2012).

Nerve cell apoptosis or necrosis and myelin disintegration occur after central nervous system injury. Activated astrocytes divide into daughter cells and proliferate, while activated microglia phagocytize disintegration products. This is identical to the axonal and myelin sheath response to peripheral nervous system injury, but the regenerative capacities of the peripheral and central nervous systems are different, mainly because of distinct nerve cell environments. Thus, the cellular environment surrounding nerve cells has a crucial effect on neural regeneration. Another main reason for inhibition of neural and axonal regeneration is the presence of abundant myelin growth-inhibitory factors in the injured axon environment, including (1) myelin-associated glycoprotein (MAG), an immunoglobulin superfamily member that surrounds myelinated axons in the central and peripheral nervous systems and can suppress neural regeneration; (2) neurite growth inhibitors (Nogo-A, Nogo-B, and Nogo-C), which inhibit nerve growth activity and contain two structural domains, Nogo-66 and amino-Nogo (Yamashita and Tohyama, 2003); and (3) oligodendrocyte myelin glycoprotein (OMgp), a specific central nervous system glycoprotein that blocks mitogenic signaling pathways and suppresses growth (Cao et al., 2010). These inhibitors act by binding to the Nogo receptor (NgR) and receptor complex (Cao et al., 2010). *NgR* gene knockout does not effectively promote axonal growth (Omoto et al., 2010), suggesting there is an NgR-like receptor (Zheng et al., 2005) that inhibits axonal regeneration. Atwal et al. (2008) identified paired

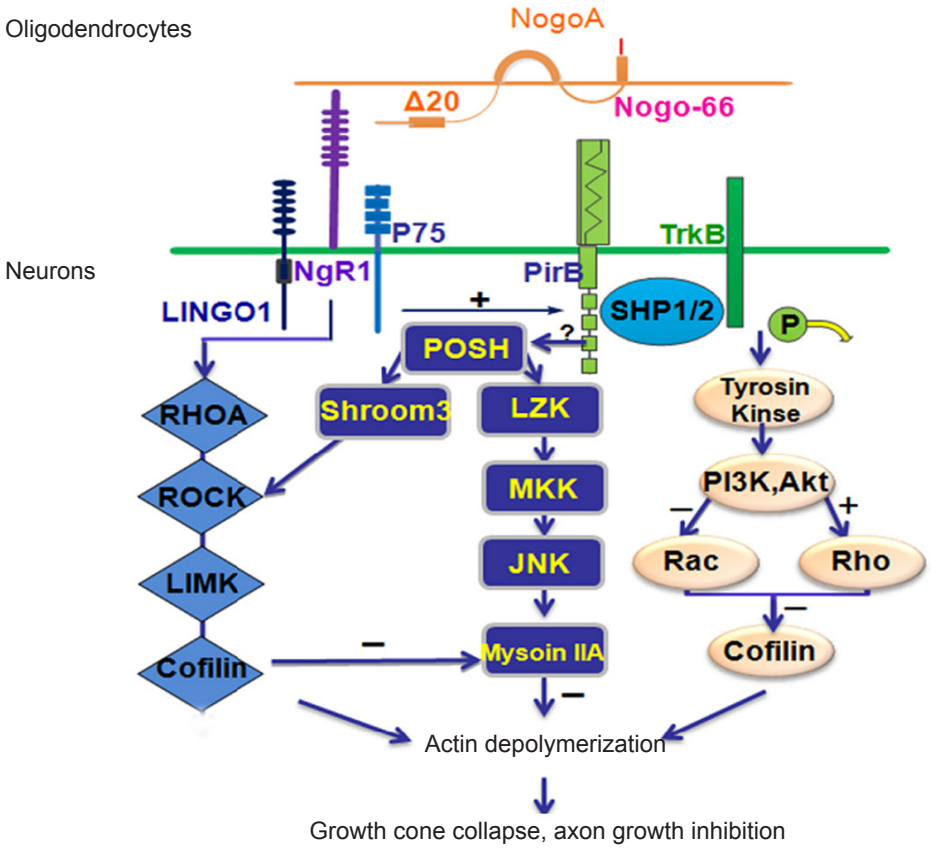

Figure 1 PirB-mediated growth cone collapse and axon growth inhibition.
A classical axon inhibition signaling pathway: Nogo on the oligodendrocyte surface binds to the NgR-LINGO1-P75 receptor complex on the neuronal membrane. Cofilin is activated by RHOA-ROCK, resulting in actin depolymerization and axonal inhibition. PirB-mediated signaling pathway: Nogo-66 binds to the PirB receptor on the neuronal membrane. (1) The Shroom3-ROCK-Cofilin and LZK-JNK-Mysoin IIA signaling pathways are activated by the POSH molecule; (2) SHP molecule recruitment leads to TrkB receptor dephosphorylation, PI3K and Akt activation, and finally results in actin depolymerization and axonal inhibition. The figure is modified from Liu et al. (2014).
PirB: Paired immunoglobulin-like receptor B; NgR: Nogo receptor; ROCK: Rho-associated coiled coil-forming protein kinase; JNK: c-Jun N-terminal kinase; SHP: Src homology containing protein tyrosine phosphatase; TrkB: tyrosine receptor kinase B; PI3K: phosphatidylinositol 3-kinase.

immunoglobulin-like receptor B (PirB) from expression cloning screening, and confirmed that it was more effective than NgR (Adelson et al., 2012). PirB is not only expressed in neurons of the central nervous system, but also regulates axonal growth and synaptic plasticity. Here, we summarize the structure and distribution of PirB, its relationship with nervous system disease, and its mechanisms of suppressing axonal regeneration. Our aim is to gain further understanding of the mechanisms of neural regeneration, and develop related studies by providing greater insight into developing methods to treat nerve injury.

Structure and Distribution of PirB

PirB (also called p91) is an immune inhibitory receptor first identified in 1997 in mouse immune cells by Kubagawa et al., and is similar to human immunoglobulin A Fc receptor (FcaR1). PIR-B protein is encoded by the single *PirB* gene that is located in the proximal region of mouse chromosome 7 and consists of 15 × 8,000 base pairs of exons (Kubagawa et al., 1997). PirB structure between rats and mice is very similar. The molecular weight of PIR-B was shown to be approximately 120 kDa by identifying glycoprotein structure on the cell surface using monoclonal or polyclonal antibodies. The PirB ligand is a major histocompatibility complex class I (MHC I) molecule (Takai, 2005). PIR-B protein is a type I transmembrane glycoprotein, but does not couple with other subunits, and has six immunoglobulin-like domains outside the cell membrane. Hydrophobic fragments are present in transmembrane domains. Four polypeptides containing immunoreceptor tyrosine-based inhibitory motifs (ITIM)-like structures are detected inside cells, which recruit Src homology region 2-containing protein tyrosine phosphatase-1 (SHP-1) or -2 (SHP-2) protein, and contribute to inhibition (Zhang et al., 2005; Matsushita et al., 2011).

PirB is distributed in various hematopoietic cells including B cells, mast cells, macrophages, neutrophils, and dendritic cells (Kubagawa et al., 1999; Kubo et al., 2009; Fan et al., 2014), and is also extensively distributed in different regions of the injured central nervous system, including the cerebral cortex, hippocampus, cerebellum, olfactory ensheathing

neurons, axon cells, neuropil, spinal cord and rubrospinal neurons (Syken et al., 2006; Filbin, 2008; Akbik et al., 2012). Atwal et al. (2008) found that PirB is not only observed in nerve cells, but is also the second neurite growth inhibitor receptor, followed by NgR. In addition, PIR-B protein has multiple homologs, and its corresponding homolog in humans is the leukocyte immunoglobulin-like receptor B2 (Takai and Ono, 2001).

Relationship between PirB and Nervous System Disease

Spinal cord injury

Spinal cord injury is a complicated pathological process. There are many unfavorable factors for axonal regeneration at the injury site including glial scarring, nerve cell injury, lack of neurotrophic factor secretion, and myelin-derived inhibitors (Nogo, OMpg, and MAG) (Nakamura et al., 2011). Zhou et al. (2010) verified by western blot assay and immunohistochemistry that PirB expression increases from day 1 to day 10 after spinal cord injury in rat models, but PirB expression is very low in the spinal cord of normal rats. Moreover, concurrent blocking of NgR and PirB, the receptors for myelin inhibition, almost completely eliminates the inhibitory effect of myelin-associated inhibitory molecules on axonal regeneration (Zhou et al., 2010). These findings suggest that PirB is strongly associated with neural regeneration after spinal cord injury.

Hypoxic-ischemic brain damage

Hypoxic-ischemic brain damage can result from various causes. Induced insufficient blood supply causes lack of oxygen and glucose supply, as well as intracellular metabolic imbalance, finally resulting in cell death through oxidative stress, inflammatory reaction, and apoptosis (Wang and Mu, 2014). Two-day-old Sprague-Dawley rat brain tissue was used to prepare primary neuronal cultures, which were then exposed to ischemia and hypoxia (Wang et al., 2012). Neurons in the experimental group were then treated with Pir-B anti-extracellular domain-specific antibody to block PirB expression. The results demonstrated a noticeable increase in neuronal axons after PirB inhibition after hypoxic-ischemic brain damage, suggesting that increased PirB suppresses axonal regeneration, and inhibiting PirB is a potential target in treatment of hypoxic-ischemic brain damage (Wang et al., 2012). Gou et al. (2013) established adult male C57BL/6 mouse models of transient focal cerebral ischemia by occluding the middle cerebral artery for 60 minutes. At 30 minutes, 2 hours, 24 hours, 3 days, and 7 days after model induction, brain tissue was obtained. RT-PCR and western blot assay confirmed *PirB* mRNA and protein expression 2 hours after transient focal cerebral ischemia that peaked at 24 hours until 7 days. Immunohistochemical staining found PirB expression mainly present in neurons of the ischemia/reperfusion penumbra, although a small number of PirB-positive cells were identified in brain tissue of normal adult mice, consistent with the western blot results. These results indicate that inhibition of axonal regeneration after ischemic stroke may be correlated with high PirB expression.

Encephalitis

Deng et al. (2012) established a model of encephalitis by injecting lipopolysaccharide (which induces the rodent inflammatory response and subsequent cognitive change) into the right hippocampi of 68 adult male rats weighing 180–200 g. Rats in the control group were injected with an equal volume of phosphate-buffered saline. Thirty days later, PirB-positive neuronal- and glial-like cells were observed in the ipsilateral hippocampus, cerebral cortex, local astrocytes, and neuronal assemblies of rats injected with lipopolysaccharide. Thus, with lipopolysaccharide induction, astrocytes in the rat cortex were activated and PIR-B protein expression upregulated. PirB was also found in partially activated astrocytes. These results indicate that after encephalitis, PirB may be involved in synaptic plasticity alterations and immunoregulation of learning and memory deficits.

Alzheimer's disease

Soluble amyloid-β oligomer weakens axonal plasticity and leads to synaptic loss-related Alzheimer's disease. Mouse PirB and the homologous leukocyte immunoglobulin-like receptor B2 are present in brain tissue, and both are amyloid-β oligomer receptors. In a transgenic mouse model of Alzheimer's disease, high PirB expression is required for the harmful effect of amyloid-β oligomer on hippocampal formation (Kim et al., 2013). Van Guilder Starkey et al. (2012) suggested that PirB plays an important role in age-related hippocampal aging (including synaptic loss and neurotransmitter release), and hippocampal function decline and aging causes cognitive dysfunction associated with Alzheimer's disease.

Retinopathy

Retinal ganglial cell apoptosis is the final pathway of various eye diseases. Many factors affect optic nerve cell apoptosis. Abundant neurite growth inhibitors play an important role in axonal regeneration in the microenvironment of injured optic nerves (Bochner et al., 2014). After monocular enucleation, PirB mutant mice show stronger visual cortical plasticity than wild-type mice (Datwani et al., 2009). PirB expression is upregulated in the mouse retina at 7 days after optical nerve injury (Wang et al., 2010). With prolonged time of optical nerve injury, PirB expression in the retina of normal and injured mice shows a gradually increasing trend at 1 hour, and 1, 3, 7, 14, 21, and 28 days after injury (Cai et al., 2012). These findings suggest that high PirB expression is a key factor for challenging axonal regeneration after optical nerve injury. In a transgenic model of Alzheimer's disease, PirB not only induced current memory loss in an adult mouse, but also mediated loss of visual cortical plasticity in adolescents (Kim et al., 2013).

Mechanisms underlying the Inhibitory Effect of PirB on Injured Nerve Regeneration

PirB as a myelin inhibitory molecule receptor exerts an inhibitory effect on neural and axonal regeneration by binding to

three myelin inhibitory molecules (MAG, Nogo, and OMgp) and the receptor MHC I molecule (Cafferty et al., 2010; Cao et al., 2010). The mechanisms are as follows:

(1) MAG interaction: MAG binds to PirB and activates SHP-1/2, which exerts its effect in the presence of p75 (Fujita et al., 2011a). SHP-1/2 inhibition may reduce dephosphorylation of MAG-induced tyrosine receptor kinase, and eliminate the MAG-mediated inhibitory effect on axonal regeneration. In nerve cells, PirB bound to tyrosine receptor kinase downregulates tyrosine receptor kinase activity in basal ganglia neurotransmitters by SHP-1/2. Axonal degeneration is induced by transfecting SHP-1/SHP-2 small interfering RNAs into mice with optical nerve damage. The above studies confirm that MAG suppresses axonal regeneration by binding to PirB.

(2) Nogo interaction: PirB binds to different structural domains of the Nogo protein, inhibiting the myelin substrate growth cone, and causing growth cone atrophy and axonal retraction (Thams et al., 2008), a classical pathway of synaptic growth inhibition (**Figure 1**). The affinities of Nogo inhibitors and PirB are different, therefore the strength of their effects is different in different cell or injury environments (Huebner et al., 2011).

(3) MHC I interaction: in the immune system, MHC I was the first identified PirB ligand, a polymorphic molecule belonging to the immunoglobulin superfamily (Shatz, 2009). Besides lymphoid tissue, MHC I is also expressed in neurons. MHC I molecules are mainly expressed in the dendrites of hippocampal neurons and proximal dendrites of Purkinje cells (Goddard et al., 2007).PirB participates in formation of immunosuppressive signals in the immune system. After MHC I binds to PirB, ITIMs in the PirB intracellular domain are phosphorylated, and recruit SHP-1/SHP-2 aggregation. The kinase further dephosphorylates Bruton's tyrosine kinase and restrains B cell activation (Pereira et al., 2004). However, the molecular mechanisms underlying PirB-mediated inhibition of cell growth and synaptic plasticity in the central nervous system remain unclear. MHC I plays a crucial effect on neural development and synaptic plasticity, and is involved in synaptic stripping. Loss of MHC I and PirB has neuroprotective effects on mouse optical nerve, but it remains unclear if MHC I molecules are required for growth cone suppression (Adelson et al., 2012). In addition, corticospinal tract projections and neuronal protection are improved in *MHC I* and *PirB* gene knockout mice subjected to stroke, compared with controls, indicating that PirB not only suppresses synaptogenesis, but can also aggravate brain injury (Cai et al., 2012; Wang et al., 2012). The detailed mechanism remains to be further confirmed.

(4) OMgp interaction: independent of p75, OMgp binds to PirB and inhibits N-methyl-D-aspartic acid receptor-dependent long-term potentiation in adult mouse hippocampus treated with p75 inhibitor (Raiker et al., 2010). Thus, PirB participates in downregulation of OMpg synaptic plasticity.

(5) p75-involved signal transmission: p75, a member of the tumor necrosis factor receptor I (TNFR I) family, participates in signal transmission of PirB. p75 inhibits axonal regeneration by mutual ligand binding between SHP-1 and SHP-2 (Fujita et al., 2011a). However, Lee et al. (2010) found that without ligand binding between both receptor types, axonal regeneration is not strengthened or improved after spinal cord injury (Lee et al., 2010). Co-immunoprecipitation studies revealed that p75 not only binds to the PirB extracellular domain, but also the intracellular domain. In the presence of myelin-associated inhibitors, the PirB/p75 interaction is strengthened. When MAG binds to PirB, p75 activates SHP-2, dephosphorylates tyrosine receptor kinase B, and inhibits axonal growth (Fujita et al., 2011b).

The mechanisms of the inhibitory effects of PirB on injured nerve regeneration are shown in **Figure 1**.

Conclusions

PirB participates in a major pathological process of the nervous system, specifically, inhibition of axonal regeneration. Similar to NgR, PirB is a receptor for an axonal regeneration inhibitor, but their roles are not identical. Here, we have summarized the structure and distribution of PirB, and its relationship with common nervous system diseases and known mechanisms, demonstrating an important role for PirB in the nervous system. Outside the nervous system, PirB is also distributed in histiocytes, *e.g.*, in the immune and hematopoietic systems. Further investigations are needed to determine if immunomodulation and blood cell migration are involved in inhibition of axonal regeneration. As a Rho–ROCK signaling pathway member, further investigations on PirB not only comprehensively improve our understanding of Rho/ROCK signaling pathway mechanisms, but also provide new ideas for the prevention and treatment of nervous system diseases.

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Conflicts of interest: *None declared.*

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