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Protein Tyrosine Phosphatase 1B: A Novel Molecular Target for Retinal Degenerative Diseases

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Abstract

Protein tyrosine phosphatase 1B (PTP1B) is considered as a major negative regulator of insulin receptor (IR) signaling. IR signaling in retina has been demonstrated to be neuroprotective. Photoreceptor specific deletion of PTP1B results in enhanced retinal IR-mediated neuroprotection indicating the importance of PTP1B as a negative regulator in the retina. Elevated levels of retinal PTP1B activity has been observed in mice lacking retinal pigment epithelium ($Rpe65^{-/-}$), a mouse model of leber congenital amaurosis (LCA-type 2), *retinitis pigmentosa* and diabetic retinopathy animal models. This enhanced PTP1B activity could down regulate the IR signaling which may contribute to the death of photoreceptor neurons and ultimately lead to retinal degenerations. The potential therapeutic agents that specifically reduce or inhibit the PTP1B activity could be beneficial in protecting or delaying the photoreceptor cell death in the retinal degenerative diseases.

XX.1 Introduction

The activity of receptor tyrosine kinases (RTKs) are regulated by the extent of phosphorylated tyrosine residues that dictate their signaling output. Protein tyrosine phosphatases (PTPs) are the major negative regulators of RTKs and their downstream effector signaling (Ostman and Böhmer, 2001). PTP1B is a prototypical member of the PTP family, considered as a direct negative regulator of several receptor and receptor-associated tyrosine kinases (Tonks, 2003; Haj et al., 2003; Stuible and Tremblay, 2010). PTP1B is widely expressed non-receptor PTP that is associated with the endoplasmic reticulum (ER) and other intracellular membranes via a hydrophobic interaction of its C-terminal targeting signal (Frangioni et al., 1992; Haj et al., 2002). Full-length PTP1B contains 435 amino acids and the catalytic domain is constituted by N-terminal residues 30-278, while the 35 C-terminal residue sequence targets the enzyme to cytosolic face of the endoplasmic reticulum (Frangioni et al., 1992; Barford et al., 1994). PTP1B dephosphorylates and inactivates several membrane receptors tyrosine kinases (RTKs) such as the epidermal growth factor receptor (EGFR) (Flint et al., 1997), the platelet-derived growth factor receptor (PDGFR) (Haj et al., 2003), the insulin receptor (IR) (Salmeen et al., 2000) and the insulin-like growth factor-1 receptor (IGF-1R) (Buckley et al., 2002). PTP1B is also involved in down regulation of JAK/STAT pathway (Cook and Unger, 2002; Myers et al., 2001; Gu et al.,

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2003). Dysregulation of PTP1B activity has been shown to contribute towards the pathogenesis of several human diseases including cancer, diabetes, obesity and immune disorders (Zhang and Zhang, 2007; Combs, 2010). The importance of PTP1B in diverse pathophysiological conditions has made PTP1B as the focus of intense interest for drug targeting.

XX.2 Importance of insulin receptor signaling in retina

Insulin receptor (IR) signaling in retina has received a considerable attention due to its importance in photoreceptor survival. Retinal neurons contain high affinity receptors for insulin (Reiter et al., 2003; Rajala et al, 2008). The IR signaling has been demonstrated as an important pathway for retinal development, physiology and survival (Rajala et al, 2008; Song et al., 2003; Barber et al., 2001). The IR activation provides a trophic signaling for retinal neurons via phosphatidylinositol 3-kinase (PI3K)/Akt pathway (Rajala et al., 2002; Barber et al., 2001). IR/PI3K/Akt signaling pathway has been shown to protect retinal neurons from anti-apoptotic mechanisms, primarily by Akt mediated phosphorylation and inhibition of many proapoptotic targets (Duke et al., 1997; Datta et al., 1999). IR signaling is also involved in 17β-estradiol-mediated neuroprotection in the retina (Yu et al., 2004). A growing body of evidence suggests that diabetic retinopathy is characterized by early onset of retinal neuronal cell death (Barber et al., 1998). Several studies have demonstrated that diabetes progressively impairs the retinal IR signaling pathway and that the loss of this survival pathway may contribute to the initial stages of diabetic retinopathy (Barber et al., 1998; Reiter et al., 2006; Rajala et al., 2009). *Retinitis pigmentosa* is an inherited retinal degenerative disease that leads to blindness and studies have shown that stimulation of insulin/mTOR pathway delays cone cell death in *retinitis pigmentosa* mouse model (Punzo et al., 2009). Studies from our laboratory for the past decade clearly show that IR and its downstream effect signaling is functionally important for both the rod and cone photoreceptor survival (Rajala et al., 2008; Ivanovic et al., 2009).

XX3. Interaction between PTP1B and IR

PTP1B has been implicated as a major negative regulator of insulin receptor signaling by dephosphorylating IR and its effector proteins (Byon et al., 1998; Goldstein et al., 1998; Dadke et al., 2000; Calera et al., 2000). The ability of PTP1B to regulate insulin-receptor kinase activity has been established at the molecular level by examining the crystal structure of PTP1B in complex with the triphosphorylated insulin-receptor kinase activation loop (Salmeen et al., 2001). The overexpression PTP1B results in the inhibition of IR signaling and the introduction of anti-PTP1B antibodies into cells enhance IR signaling (Ahmad et al., 1995). A number of systemic and tissue specific mouse models of PTP1B deficiency have confirmed its physiological effect on insulin sensitivity and high fat diet-induced weight gain (Elchebly et al., 1999; Klaman et al., 2000; Bence et al., 2006; Delibegovic et al., 2009). Neuronal PTP1B has also been shown to regulate body weight, adiposity and leptin action (Bence et al., 2006). The expression, activity and functional role of PTP1B activity in the retina has been well documented (Rajala et al., 2009; Rajala et al., 2010). Interestingly, the photoreceptor specific deletion of PTP1B resulted in enhanced IR survival signaling. These studies indicate that the IR activation in photoreceptor cells is regulated by PTP1B activity (Rajala et al., 2010).

XX.4 Implication of PTP1B activity in retinal diseases

In retina, the PTP1B activity is regulated in a light dependent manner through photobleaching of rhodopsin (Rajala et al., 2010). One of the important issues in the retina research is how the mutations in human rhodopsin gene slowly disable and eventually disrupt the photoreceptor function and survival. Defects in the photobleaching of rhodopsin and mutations in the rhodopsin gene enhance the activity of PTP1B. This enhanced PTP1B

activity may contribute to the progression of retinal degenerations. Further, the PTP1B activity is also elevated in Rpe65$^{-/-}$mice, a mouse model of leber congenital amaurosis (LCA-type 2) (Rajala et al., 2010). *Retinitis pigmentosa* (RP) is one of the most common forms of inherited retinal degeneration and an elevated PTP1B activity in RP models has also been observed (Rajala et al., 2010). Decreased retinal IR signaling has been observed in the diabetes (Barber et al., 1998; Reiter et al., 2006; Rajala et al., 2009). This reduction of IR signaling is associated with the increased PTP1B activity in diabetes (Rajala et al., 2009). In addition, PTP1B is known to act as negative regulator of JAK/STAT pathway (Myers et al., 2001; Gu et al., 2003). This pathway also been demonstrated as neuroprotective signal in light-stress induced degeneration models (Samardzija et al., 2006; Ueki et al., 2009). The dysregulation of PTP1B activity may contribute to the death of retinal neurons and ultimately lead to retinal degeneration.

XX.5 PTP1B as a therapeutic target

PTP1B has been considered as a suitable target in the resolution of several disease pathologies. It is a preferred target for diabetes and obesity treatments (Zhang and Zhang, 2007; Combs, 2010). In order to effectively target this protein in alleviation of retinal pathologies mediated through its high activity it is essential to have a thorough understanding of the structure, physiological mechanism of action and regulatory control of this enzyme. It is essential that the drug used specifically discriminates between the PTP1B and other phosphatases, most of which act by similar catalytic mechanisms and exhibit a striking similarity in their active sites and structures. The resolution of crystal structures in complex with IR (Salmeen et al., 2001) and EGFR (Jia et al., 2001) has enabled in understanding its mechanism of action to a great extent. The requisite inhibitor(s) should be targeted to both active site and the secondary binding regions in such a way that it achieves a unique selectivity amongst the tyrosine phosphatases but without significantly compromising their potency (Combs, 2010). The post-mitotic nature of the retina and the presence of blood retinal barrier necessitates that the potential drug has minimal toxicity and high pharmacodynamic turn-over rate in eye. Genetic engineering to promote the expression of physiological inhibitors of PTP1B may be the best strategy but considering the practical limitations and lack of complete knowledge of retinal physiology, administering a selective potential PTP1B peptide mimetic inhibitor or antisense oligonucleotides may be a step forward to rescue or delay the photoreceptor cell death in retinal degenerative diseases. Consistent with this idea that we recently reported that intravenous injection of an allosteric inhibitor of PTP1B protects the rats against light stress induced retinal degeneration through the protection of IR phosphorylation (Rajala et al., 2010).

XX.6 Conclusions

PTP1B has emerged as the best-validated drug target for diabetes and obesity. PTP1B is considered as a major negative regulator of IR and JAK/STAT signaling, which have been demonstrated as neuroprotective pathways in retina. The emerging understanding of retinal physiology indicates that phototransduction is integrated with the receptor tyrosine kinase survival signaling. Defects in phototransduction can either manifest their effects or their effects might be aggravated through the key players in receptor tyrosine kinase signaling. This is coupled with the fact that enhanced PTP1B activity has been associated with several retinal degenerative diseases. All these observations steer us to an understanding that PTP1B is an extremely important regulatory valve whose malfunction can lead to severe degenerative phenotypes and the key role of this enzyme provides an opportunity to manipulate its *in vivo* properties and thereby regulate several phenotypes which are mediated through its malfunction.

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