Review

Protein tyrosine phosphatases PTPδ, PTPσ, and LAR: presynaptic hubs for synapse organization

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Synapse development requires differentiation of presynaptic neurotransmitter release sites and postsynaptic receptive apparatus coordinated by synapse organizing proteins. In addition to the well-characterized neurexins, recent studies identified presynaptic type IIa receptor-type protein tyrosine phosphatases (RPTPs) as mediators of presynaptic differentiation and triggers of postsynaptic differentiation, thus extending the roles of RPTPs from axon outgrowth and guidance. Similarly to neurexins, RPTPs exist in multiple isoforms generated by alternative splicing that interact in a splice-selective code with diverse postsynaptic partners. The parallel RPTP and neurexin hub design facilitates synapse self-assembly through cooperation, pairs presynaptic similarity with postsynaptic diversity, and balances excitation with inhibition. Upon mutation of individual genes in neuropsychiatric disorders, imbalance of this synaptic organizing network may contribute to impaired cognitive function.

Introduction

The RPTPs are a large protein family with eight subtypes based on diverse extracellular domains [1,2]. The type IIa RPTPs, composed of three members in vertebrates, leukocyte common antigen-related (LAR), PTPσ, and PTPδ, contain typical cell adhesion immunoglobulin-like (Ig) and fibronectin III (FNIII) domains, suggesting the involvement of RPTPs in cell–cell and cell–matrix interactions [2–4]. Studies on the roles of RPTPs in the central nervous system (CNS) had initially focused on axon outgrowth, guidance, and regeneration [1,2,4]. More recently, however, many cell biology studies have demonstrated novel roles of RPTPs as presynaptic proteins that trans-synaptically interact with multiple postsynaptic partners to mediate synaptic adhesion and synapse organization [5–12]. These RPTP-based complexes act in a similar manner and often in parallel with complexes of presynaptic neurexins with postsynaptic neuroligins, leucine-rich repeat transmembrane neuronal proteins (LRRTMs), or cerebellin–glutamate receptor-δ (GluRδ) [13–15]. Furthermore, despite a lack of structural homology or common postsynaptic binding partners, RPTPs and neurexins share a key organizational feature: alternative splicing of each of these presynaptic protein families controls their affinity of interaction with multiple postsynaptic binding partners. In other words, both RPTPs and neurexins display splice-selective binding codes with diverse postsynaptic partners. Accumulating evidence indicates that these two parallel synapse organizing pathways cooperate in the development of many synapses and are linked through presynaptic and postsynaptic intracellular pathways. Further, the genes encoding RPTPs and their postsynaptic partners are associated with neuropsychiatric disorders including autism and schizophrenia [16–20], as are like deleterious mutations in the genes encoding neurexins and partners [13,21], supporting the possibility that aberrant synaptic organization might be a fundamental pathogenesis of neuropsychiatric disorders. We review recent evidence for trans-synaptic interaction between presynaptic RPTPs and their multiple postsynaptic partners and the functions of these complexes in synapse development. Further, we discuss the possible physiological significance of the apparent hub design of RPTP-based as well as neurexin-based synapse organizing complexes.

Structure of RPTPs

LAR, PTPσ, and PTPδ are encoded by three independent genes and share overall 66% amino acid identity [22]. Each contains extracellular Ig and FNIII domains, modified by alternative splicing, which mediate diverse extracellular protein interactions. By contrast, RPTP intracellular protein interactions are less diverse and involve the two intracellular protein tyrosine phosphatase (PTP) domains, the membrane-proximal D1 domain with robust catalytic activity and the membrane-distal D2 domain with residual or no catalytic activity [2–4] (Figure 1). RPTPs undergo constitutive proteolytic processing generating an extracellular subunit that remains noncovalently bound to the phosphatase domain subunit [4], but the

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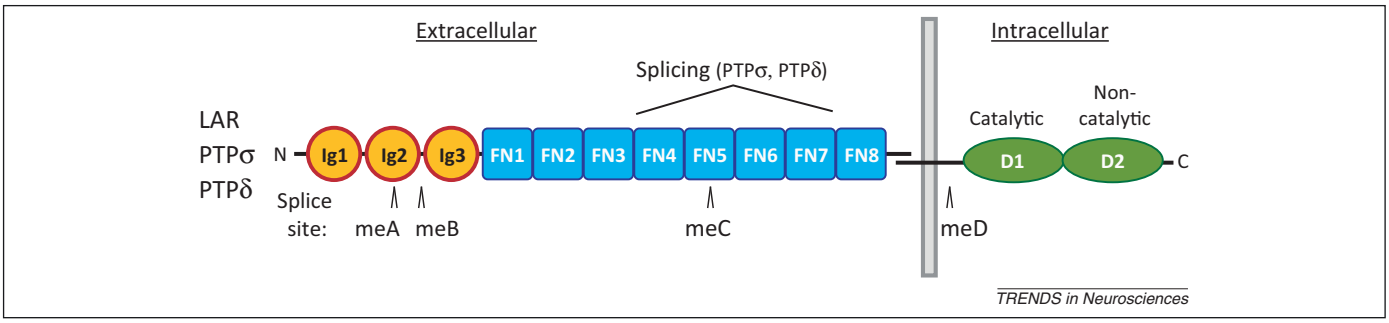

Figure 1. The structure of type IIa receptor-type protein tyrosine phosphatases (RPTPs). Each RPTP contains three extracellular immunoglobulin (Ig)-like domains followed by four or eight fibronectin III (FNIII) domains, depending on alternative splicing, and two intracellular protein tyrosine phosphatase (PTP) domains, the membrane-proximal D1 domain with robust catalytic activity and the membrane-distal D2 domain with residual or no catalytic activity [2–4]. The additional multiple isoforms of RPTPs are generated by alternative splicing of four mini-exons (meA–meD) encoding short amino acid peptides [22,97]. The meA insert with nine or fewer residues is located in the second Ig domain (Ig2), presumably affecting the length of a loop region between the D and E β-strands of Ig2, whereas the meB insert with four residues is located at the end of Ig2 [22,97,98]. The two *Drosophila* orthologs DLAR and DPTP69D and the single *Caenorhabditis elegans* ortholog PTP-3 also have two intracellular PTP domains but differ in the number of extracellular Ig and FNIII domains [2,4,31]. The site of constitutive proteolytic processing that generates an extracellular subunit (E-subunit), which remains noncovalently bound to the phosphatase domain subunit (P-subunit) [4], is also indicated.

functional significance of this modification is not clear. RPTPs can also undergo regulated ectodomain shedding by cleavage at an independent site [23], a mechanism that might be used to curtail the synapse organizing activity of RPTPs.

Hub design of RPTPs: multiple trans-synaptic binding partners

Recent studies demonstrate that presynaptic RPTPs make trans-synaptic adhesion complexes with multiple postsynaptic binding partners to regulate synapse organization. These studies first identified many novel postsynaptic adhesion molecules that can induce presynaptic differentiation in a trans-synaptic manner, here called 'synaptic organizers' or 'synaptogenic' proteins, through a fibroblast–neuron co-culture assay [24,25]. In this assay, synaptogenic proteins expressed on the surface of nonneuronal cells trigger formation of functional neurotransmitter release sites in contacting axons of co-cultured neurons. Intriguingly, many of these studies consequently identified RPTPs as presynaptic receptors of the synaptogenic proteins. The postsynaptic binding partners of RPTPs in trans-synaptic complexes have been identified so far as follows (Figure 2): netrin-G ligand-3 (NGL-3) [5,6], neurotrophin receptor tropomyosin-related kinase C (TrkC) [7], interleukin-1-receptor accessory protein-like 1 (IL1RAPL1) [8,9], interleukin-1 receptor accessory protein (IL1RAcP) [10], and Slit and NTRK-like family (Slitrk 1–6) [11,12].

Each synaptic organizer displays an individual code in terms of selectivity for RPTP binding (Figure 2). NGL-3 binds to LAR, PTPσ, and PTPδ through their first two FNIII domains [5,6]. TrkC binds selectively to PTPσ, IL1RAPL1 selectively to PTPδ, IL1RAcP to LAR, PTPσ, and PTPδ, and Slitrks selectively to PTPδ and PTPσ, through the Ig domains of the RPTPs [7–12]. Importantly, alternative splicing at the meA and meB sites regulates the affinity of interaction of the RPTPs with all of these partners except for NGL-3. Thus, RPTPs may be considered a presynaptic hub for coupling to diverse postsynaptic partners.

A similar hub design has emerged for neurexins: distinct presynaptic neurexin isoforms generated from different genes, alternative promoters, and alternative splicing bind to distinct postsynaptic partners [13–15]. The parallel design of RPTP and neurexin hubs is striking, very different in nature from cadherin superfamily interactions in which isoform-selective homophilic interactions predominate and contribute to processes such as target recognition and dendritic self-avoidance [26]. However, control of diverse extracellular partnerships by splice-selective binding codes appears to be a feature of Ig superfamily proteins other than RPTPs such as the L1/neuron-glia cell adhesion molecule (NgCAM) family [27,28], and thus may be a more general mechanism. The possible physiological and pathological significance of this hub design of RPTPs as well as neurexins is discussed in Box 1.

Functions of RPTPs in synaptic organization

RPTPs in trans-synaptic complexes have three general functions in synaptic organization (Figure 3). One is to mediate cell–cell adhesion at synapses. The second is to mediate presynaptic differentiation, local recruitment of synaptic vesicles and release and recycling machinery, a form of retrograde synaptogenic signaling triggered by binding of the postsynaptic partner to axonal RPTPs. The third is to trigger postsynaptic differentiation, local recruitment of neurotransmitter receptors, scaffolds, and signaling proteins, a form of anterograde synaptogenic signaling triggered by binding of the presynaptic RPTP to dendritic binding partners. A function of postsynaptic RPTPs has been also reported [29], and the RPTP complexes reviewed here may well participate in regulating axon guidance and target specificity [2]. However, this review focuses on the functions of RPTPs as presynaptic components of synaptic organizing complexes and the associated retrograde and anterograde signaling pathways.

RPTP functions in synapse organization were first indicated by genetic studies in invertebrates. *Drosophila* DLAR and *Caenorhabditis elegans* PTP-3 mutants show altered presynaptic organization affecting vesicles and active zones [30,31]. Based on expression patterns and phenotypes of mutant mice [4] as well as recent studies of RPTP-based complexes as detailed below, PTPσ and PTPδ may be more important than LAR for synapse organization in vertebrates. In adult brain, LAR shows weak expression whereas PTPσ and PTPδ are highly expressed, PTPσ very broadly, and PTPδ particularly strongly in