RPTPs in axons, synapses and neurology

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Abstract

Receptor-like protein tyrosine phosphatases represent a large protein family related to cell adhesion molecules, with diverse roles throughout neural development in vertebrates and invertebrates. This review focuses on their roles in axon growth, guidance and repair, as well as more recent findings demonstrating their key roles in pre-synaptic and post-synaptic maturation and function. These enzymes have been linked to memory and neuropsychiatric defects in loss-of-function rodent models, highlighting their potential as future drug targets.

Introduction

Receptor-like protein tyrosine phosphatases (RPTPs) were discovered in the late 1980's and are classified according to ectodomain structures [1]. Many are still being orphan receptors. Due to their developmental expression patterns, these phosphatases soon became a focus of interest in developmental neurobiology. A great deal has now been learnt about the expression, structures and cellular functions of these enzymes. Here we will explore both historical and recent research in three broad areas of RPTP function: (i) axon growth, guidance and regeneration; (ii) synaptogenesis and plasticity; (iii) neurological disorders and disease (Figure 1). As we are restricted for space, the reader will be referred to several excellent, focussed reviews that cover these individual areas.

1. RPTPs in axon growth, guidance and regeneration

RPTPs have long been implicated in the control of axon growth and guidance. Several excellent reviews are published with more detailed information [2-5].

1.1 Drosophila RPTPs

Drosophila has 6 RPTP genes, DLAR, DPTP69D, DPTP10A, DPTP99A, DPTP52F, DPTP4E, only three of which have clear mammalian orthologues [1]. Each influences the growth and guidance decisions of several stereotypical axonal pathways in the embryo stage of Drosophila development [3]. These have been studied largely in CNS longitudinal fascicles, the neuromuscular system (ISN and SN nerves and their targets), mushroom body neurons and in photoreceptor axon guidance. These have highly reproducible axon growth and guidance programmes that are amenable to genetic manipulation. Fly RPTPs

control growth cone fasciculation to nerve tracts, defasciculation at choice points, recognition of targets, and establishment of stable synaptic contacts. Where directly investigated, RPTP ectodomains have been shown to be essential for these roles, whereas active catalytic domains are not always necessary. For example, DPTP69D controls choice point de-fasciculation of SNb axons requiring catalytic function [6]. In contrast, ommatidial R7 axon targeting requires DLAR, but not its catalytic capacity [4, 7]. The general conclusion is that both the adhesive functions and catalytic function of RPTPs can play important roles in axonal development, working alongside other well established adhesion and signalling systems. Several studies demonstrate that the 6 fly RPTPs have some functional redundancy, but can also synergise and counteract each other [8-12]. These relationships differ depending on which axon guidance model is studied and Jeon has proposed a network of potential interactions [10] (adapted in Figure 2).

Ligands have been identified for DLAR and PTP10D. DLAR functionally interacts with proteoglycans during synapse formation [13] (see below) and during ISNb motor axon guidance [14]. DLAR also interacts in trans with cadherin to control targeting of R1-R6 photoreceptor axons to the optic lobe lamina [15]. This latter interaction requires the pre-synaptic, intracellular interaction of DLAR with liprin-α, but does not necessitate catalytic activity in DLAR. A ligand has recently been identified for PTP10D. Sas, a membrane protein expressed in most CNS cells [16, 17] binds specifically to PTP10D in trans, supporting a functional interaction that prevents unnecessary midline crossing of commissural axons. Interestingly the distinct midline axon phenotype of *Ptp10D Ptp69D* double mutants can be partly mimicked by *Sas Ptp69D* double mutants, supporting the conclusion that Sas is indeed a Ptp10D ligand. The signaling downstream of DPTP10D also appears to be shared with Ptp69D.

1.2 Vertebrate RPTPs.

There are 21 mammalian RPTPs. Here we limit discussion to those RPTPs most clearly implicated in nerve growth, guidance or regeneration (Figure 1). The type IIB RPTPs are discussed in detail elsewhere in this volume.

Type IIA RPTPs. All three type IIA RPTPs, PTPσ, PTPδ and LAR, influence the outgrowth of neurites and axons in cell culture models and in vivo [2]. These RPTPs are immunoglobulin (Ig) superfamily cell adhesion molecules, with alternative isoforms generated through differential mRNA splicing. Such isoforms can have quite distinct ligand binding properties, which will in turn likely affect the degree and specificity of influence over neurite behaviour. All three RPTPs can promote neurite outgrowth in a

cultured retinal neurons [18], hippocampal neurons [19, 20] and PC12 cells [21]. These experiments demonstrated neurite promotion non-cell-autonomously [18, 20] by isolated ectodomains from these RPTPs, as well as cell-autonomously through endogenous RPTP actions [21].

To effect such neurite control, RPTPs need ligands. Of particular interest are the proteoglycan ligands of PTPσ. Both heparin sulphate proteoglycans (HSPGs) and chondroitin sulphate proteoglycans (CSPGs) bind to PTPσ and these ligand classes may have opposite influences over axon elongation [22]. Specifically, HSPGs are proposed to induce PTPσ dimers, inactivating catalytic function and facilitating axon elongation. In contrast CSPGs may force PTPσ monomer formation, enzyme activation and signals that inhibit growth cone movement [22]. The structural basis for these interactions has been ascertained and is discussed in (**see Coles chapter**). Interestingly, there is an evolutionary correlate of these findings in *Drosophila*, since DLAR, the orthologue of mammalian type IIA enzymes, binds HSPGs Dally-like and Syndecan, eliciting distinct effect on synapses (see below).

In *Xenopus* all three type IIA RPTPs can influence retinal axon guidance [23] . In the chick embryo model, the outgrowth of the hindlimb anterior iliotibialis nerve is stunted when PTPσ and PTPδ expression is knocked down with siRNA in ovo (and the type III PTPRO; see below) [24]. In the chick model once again, PTPσ was shown to control the outgrowth and targeting of the optic axons to their tectal targets [25]. Although mice lacking PTPσ do not show evidence of axon guidance defects, loss of function (LOF) of PTPσ and PTPδ reveals a synthetic genetic relationship[26]. When both RPTPs are depleted, the phrenic nerve innervating the diaphragm initially extends normally to its target, but then fails to maintain contact and degenerates. This indicates redundant actions of these RPTPs, in a very specific axonal context. It is unclear why other nerves that co-express these RPTPs are not affected, but further levels of redundancy with other RPTPs cannot be ruled out.

Type III RPTPs.

PTPRO. SiRNAs targeting *Ptpro* in the chick embryo caused aberrant outgrowth of the dorsal hindlimb motor nerve[24], including complete loss of the nerve, poor outgrowth or fasciculation defects. These are greater effects than seen with siRNAs specific for PTPσ and PTPδ [24]. Combinations of siRNAs treatments demonstrate that PTPδ partially suppressing the PTPRO LOF phenotype. This was the first demonstration that vertebrate type III and type IIA RPTPs can counteract each other's actions in axon growth and guidance, paralleling findings with DPTPs (see above; Figure 2).

PTPRO has also been implicated in controlling axon guidance in the avian visual system [27]. PTPRO can enzymatically target and suppress the signalling capacity of Ephrin receptors EPHA and EPHB, which in turn modifies axon guidance. When PTPRO is experimentally suppressed in cultured retinal axons, this leads to hypersensitivity to ephrins. In ovo, PTPRO suppression leads to retinotopic projection defects and failure to arborize with tectal targets. This phosphatase is therefore required for retinal axon growth and target recognition, acting through Ephrin/EPH pathways. PTPRO may therefore act alongside PTPσ in guiding retinal axons [25]. Lastly , in mice lacking PTPRO, there is evidence of defective spinal axon guidance [28].

Type V RPTPs

PTPγ. PTPγ is expressed widely in the nervous system, both centrally and peripherally [29]. Animals deficient in *Ptprg* develop with anatomically fairly normal nervous systems, although behavioural changes are observed [30, 31] (see below). In the chick embryo model, this phosphatase is implicated in spinal neurogenesis [32]. More recently PTPγ has also be implicated in the neurite outgrowth of rat cortical neurons [33].

The influence of PTPγ over neurite outgrowth appears to be founded on its interactions with contactins, a family of GPI-anchored adhesion molecules [34, 35]. PTPγ binds to contactins 3, 4, 5 and 6 via its carbonic anhydrase-like N-terminal domain, whereas the closely related PTPζ binds only contactin1 [34]. For PTPγ, the role of these contactin interactions has remained uncertain. However, secretion of soluble forms of contactins 4,5 and 6 in co-cultures show that these can increase neurite length, branching and number of neurites per cell in cortical neurons, although these effects were modest and apparently transient [33]. Contactins, as well as PTPγ, can be cell-associated or shed from cell surfaces [36, 37] and the physiological consequences of these potentially complex PTPγ-contactin interactions remain to be determined in vivo. Contactins may also share PTPα as a binding partner [38]. Thus although mice lacking *Ptprg* do not show obvious nerve development problems, subtle problems with nerve network formation during development may give rise in part to the behavioural defects observed [30, 31].

PTPζ. PTPζ is related closely to PTPγ and its gene encodes several protein isoforms, including a major secreted isoform, phosphacan. Because of this, different isoforms can have cell-autonomous or non-cell-autonomous actions over neurite formation. For example, it can have a cell-autonomous, suppressive effect over NGF-induced neuritogenesis in PC12 cells. This is thought to operate through tyrosine

dephosphorylation of the neurotrophin receptor TRKA [39]. PTPζ is also thought to send signals in trans (non-cell-autonomously) to neurons, through neuronal contactin and NrCAM. This stimulates neurite outgrowth from chick tectal cells [40]. PTPζ binds to contactin1 selectively, distinguishing it from the contactin ligands of PTPγ [34, 41, 42]. PTPζ also has pleiotropin as an extracellular ligand and there is a suggestion that this interaction directly influences neuritogenesis. This effect may be somewhat indirect though [43], as may be the proposed ability of PTPζ to direct morphogenesis of dendritic spines on Bergmann glia [44]. In *Xenopus*, cranial nerve elongation and fasciculation are defective after overexpression of various PTPζ isoforms [45]. However, again these effects may well be non-cell autonomous, since the secreted form of PTPζ was equally effective. The physiological relevance of such overexpression approaches has also to be treated with caution.

Mice deficient for the *Ptprz* gene develop apparently normally [46]. Nevertheless, it is feasible that effects might by masked by the compensatory actions of other PTPs. In summary, the role of PTPζ isoforms in neural development is complex, positioned as it is on both neurons and glia and with major transmembrane and secreted isoforms with distinct roles [47] (**see Harroch chapter**).

1.3 RPTPs and Nerve regeneration.

With their roles in axon growth and guidance, it is unsurprising that RPTPs influence the regeneration of nerves, with PTPσ being of particular interest. PTPσ-deficiency leads to increased sciatic nerve repair in mice (albeit with local guidance errors) [48], better optic nerve regeneration after nerve crush [49], and improved facial nerve regeneration [50]. Corticospinal tract regeneration is also improved in the absence of PTPσ, and cultured cerebellar granule neurons show reduced inhibition by CSPGs [51]. In contrast, type IIA LAR-deficiency appears to lead to reduced sciatic regeneration [52, 53]. Looking at type V RPTPs, remyelination is defective in PTPζ-deficient mice, although this may be largely an oligodendrocytic role [54].

2.0 RPTPs in in synaptogenesis

2.1 Pre-synaptic roles. RPTPs remain strongly expressed in the nervous system after their requirements during axon growth and guidance events have finished. Thereafter, we now know that a major role resides in the synapse. The first clue came in 2006, when *Drosophila* DLAR was shown to bind the HSPGs Dally-like and Syndecan. These interactions regulated either presynapse formation (Syndecan:Dlar), or remodeling of active synapses (Dally-like:DLAR) [13]. Mammalian LAR was soon implicated in synapse

formation in hippocampal neurons [55]. More recent research of presynaptic PTPσ in zebrafish shows that PTPσ prevents excessive numbers of synapses from forming in terminals of olfactory sensory neurons, but it does not actually control normal synapse formation [56]. Given these indications of synaptic roles, it is gratifying to now see a number of key synaptic partners identified for these RPTPs, cementing their importance as synaptic regulators. As this area is fast moving and has been reviewed recently [57-59], we will give only an overview.

In 2009, Woo discovered that LAR expressed in Cos7 cells can trigger presynaptic maturation in co-cultured hippocampal neurons. This was through interaction of LAR FNIII domains with netrin-G ligand–3 (NGL-3) [60]. NGL3 is expressed widely in neurons and is a postsynaptic adhesion molecule that complexes with PSD95 [61]. PTPσ can also interact with NGL-3 to promote synapse formation bidirectionally, and PTPδ-NGL-3 interactions promote pre-synaptic maturation unidirectionally [62]. Furthermore, PTPδ has recently been shown to bind to ILRap1 [63, 64], PTPσ binds to synaptic neurotrophin receptor TRKC [65], PTPσ and PTPδ bind to Slitrk synaptic proteins of the leucine rich repeat family [66-68] and all three type IIA RPTPs bind to synaptic IL1RAcP (PTPδ the strongest [69]). In Takahashi's comprehensive review, these multiplex interactions are described as synaptic hubs, akin to those found with neurexins and neuroligins [70]. Such hubs may facilitate a range of diverse pre- and post-synaptic responses, in both excitatory and inhibitory synapses. Certainly there is ample opportunity for these RPTPs to interact with individual or multiple trans-synaptic partners, as adhesion molecules, clustering complexes and pre-synaptic phosphatase signalling centres. The structural basis for the extracellular interactions and their modulation by splicing is discussed further in chapter N (**Coles**)

The TRKC interaction with PTPσ is interesting given that type IIA RPTPs are also cis interactors of TRKs and regulators of TRK signalling [71, 72]. As NT3 binds to TRKC using different domains than PTPσ, it remains to be seen how NT3 may influence, or be influenced by, TrkC-RPTP interactions.

The interactions of RPTPs with a growing number of postsynaptic partners, points to a potential range of diverse, combinatorial and dynamic signaling. This would sit perfectly with the requisite dynamics of synaptic plasticity. Further modulation of trans-synaptic interactions by alternative splice variations of the RPTPs, may provide another level of post-transcriptional control. For example in the ectodomain of type IIA RPTPs, alternate mini-exons named meA and meB in the immunoglobulin domains are

able to determine the affinity of interactions with TRKC, IL1rAP and Slitrks [57, 64, 69]. RPTP interactions in synapses may also be modulated by local interactions HSPGs and CSPGs [22, 73], in a similar vein to that found with Drosophila DLAR [13]. These interactions may be significant given that mammalian dendritic spines and synapses are clearly influenced by proteoglycans [74, 75]. Since proteoglycans and TRKC have overlapping binding sites on PTPσ, the proteoglycans could well modify RPTP-dependent trans-synaptic signals, by interfering with TRKC binding (**see also Coles chapter**).

Further signaling complexity may arises from the release of cell surface RPTP ectodomains through gamma secretase action [76, 77] (Figure 1). Gamma secretases are proteases within synapses with relevance to diseases such as Alzheimer's [78]. Indeed they act upon NGL3 to influence LTD in brain slices [79]. If gamma secretase regulation is central to the rapid modulation on intra-synaptic hubs, then the RPTPs are very likely to be targeted as well. RPTP ectodomain shedding could then be part of either a down-regulation pathway, or the solubilized ectodomains could themselves act locally to modulate other synaptic interactions.

2.2 Pre-synaptic signaling. In the pre-synaptic active zone, it appears that type IIA RPTP help to promote differentiation and recruitment of pre-synaptic vesicles. How RPTPs do this is largely unclear, but there is definitely one link from RPTPs to vesicular control through the multidomain scaffolding protein Liprin-α [80]. Established largely in *Drosophila* and *C.elegans*. model systems, Liprin-α may be the crucial link from type IIA phosphatases to partners such as CASK and RIM, enabling control of active zone dynamics (reviewed in [81]).

2.3 Post-synaptic roles. RPTPs also function in post-synaptic membranes (reviewed in [59]). LAR is implicated in the delivery of cadherins and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to nascent excitatory synapses, possibly through a scaffolding role with liprin-α, β-catenin and GRIP [55]. Once in the synapse, LAR is also believed to control phosphorylation of AMPAR, leading to AMPAR internalization and contributing to LTD. LAR can also associate with PSD95 and may have a broader role in dendritic spine formation. This is supported by the fact that RNAi-induced reduction in LAR, or in fact any of the type IIA RPTPs, leads to reduced dendritic spine numbers and AMPAR GluR2 density in hippocampal neurons [55]. For type IV RPTPs, PTPα is a positive regulator of post-synaptic NMDA receptor subunits NR2A and

NR2B, wherein the PTP activates SRC family and PYK tyrosine kinases, leading to increased NMDAR phosphorylation and activation [82]. Other RPTPs may potentially modulate other post-synaptic receptors in cis, including TRKC for example, given its interactions with type IIA RPTPs and PTPRO [71, 83].

3. RPTPs in memory, synaptic function and neurological disorders

In 2006 it was shown that *Drosophila* rely on PTP10D to control long term memory, specifically within mushroom bodies, and that this ongoing function was required for plasticity during memory formation itself. In other words, it showed that memory deficits were not caused by an earlier, neurodevelopmental defect [84]. Most engineered mouse strains that have germline loss of RPTP genes, although outwardly normal in many cases, later revealed subtle learning and behavioural deficits (Table 1) [57]. In the following examples, it should noted that it remains largely unclear what proportion of each phenotype is caused by on-going, synaptic dysfunction, or an underlying developmental defect of mis-wiring.

PTPδ. Without PTPδ, mice suffer memory deficits in maze tasks. Long-term potentiation (LTP) induced in hippocampal synapses is also enhanced [85]. Genetic evidence in humans points to PTPδ being involved in restless legs syndrome and in attention-deficit hyperactivity disorder (ADHD) [57, 86, 87].

LAR. Loss of LAR catalytic domains in the mouse germline leads to mild spatial learning defects and some increase in nocturnal activity [88].

PTPRO. PTPRO-deficient mice have nociceptive deficits. However, these may be caused by developmental loss of sensory neurons and nociceptive circuits, rather than a PTPRO-dependent synaptic dysfunction [28].

PTPγ. PTPγ-deficiency causes mild behavioural changes including poor, cued fear conditioning and altered processing of acoustic stimuli [31]. A later study revealed anti-depressant-like behaviours [30]. This is of interest since genetic lesions in contactin genes, encoding PTPγ ligands, are implicated in autism spectrum disorders [89].

PTPζ. PTPζ-deficiency leads to some age-related impairment in motor performance and skills development, and reduced nociceptive responses [90]. There is also enhancement of LTP, potentially functioning through dephosphorylation of RhoGAP by PTPζ, affecting Rho GTPase action [91].

PTPα. Mice lacking PTPα have significant deficiencies in LTP in CA1 pyramidal neurons [92, 93]. They have learning and neuroplasticity defects, but their behaviour is otherwise largely similar to wild type mice.

Of great interest for the type IIA enzymes is the fact that ligand genes including *SLITRKs*, *TRKC* and *IL1RAPL1*, have each been genetically implicated in neuropsychiatric disorders in man (reviewed in ref. 58). The extent to which the RPTPs themselves might influence these neuropsychiatric phenotypes in humans remains to be seen, but the possibility that these could be translated into therapeutic strategies is an enticing prospect.

Conclusion

RPTP enzymes are now functionally recognised in controlling axonogenesis as well as synapse structure and function. The elegant complementarity between their developmental and adult roles, highlights how proteins are re-deployed during ontogeny. How multiple RPTP members co-exist in individual neurons in a balanced regulatory network [94] and how this might influence drug targeting strategies, are key questions. Nevertheless, their influence over nerve regeneration could prove highly relevant to CNS trauma treatment. Moreover, with their potential links to neuropsychiatric disorders, RPTPs could represent an exciting new class of therapeutic targets.

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Figure Legends

Figure 1

Schematic structures of vertebrate RPTPs, with protein sub-domains indicated. Where secreted or cleaved ectodomains are documented, these are shown to the left of the full-length proteins. The known roles of these RPTPs are indicated for (i) synaptic development or plasticity, (ii) axon guidance, or (iii) axon elongation and regeneration.

Figure 2

Genetic interaction between pairs of RPTPs in *Drosophila*, chick and mouse. Gene names, their relationship to vertebrate orthologues and their tissue location are indicated for fly RPTPs (NCO: no clear vertebrate orthologue, see Andersen 2005; A, axons only; A+N, axons plus neuronal cell bodies; broad, broad embryo expression). **Panel A**, adapted from Jeon et al. [10]. Doubleheaded arrow indicates synthetic genetic relationship; single arrows indicates enhancement of genetic effect, or cooperation; blunt ends indicate genetic suppression. Thicker lines indicate larger effects. Blue dashed lines indicate RPTP interactions in motor axons, black lines indicate longitudinal axon interactions. **Panel B**, Genetic interactions in spinal motor nerves in the chick (mutual suppression of phenotype [24]), or in phrenic nerves in mice (synthetic interaction [26]).

Table 1

RPTP	neurite growth & regeneration	axon guidance	synapse formation & plasticity	behavioural changes in gene-deficient mice	ligand*	cis partners/ effectors in neural cells	refs
PTPα	rodent		*rodent*	Modest learning and neuroplasticity deficits; LTP deficit		NCAM, FGFR, FYN, SRC, PYK, CaMKIIalpha, GRB2, PSD95	[92, 93, 95-97]
PTPζ¶	*Xenopus, rodent*			Enhanced LTP; memory deficits	Contactin, Pleiotrophin	TRKA	[33, 34, 39-43, 45, 90]
PTPγ	rodent			Anti-depressive behaviour; reduced fear conditioning responses	Contactins 3-6	β-catenin p13(suc1)	[30, 31, 34, 98]
PTPδ	*Xenopus*, rodent, man	rodent	*rodent*	Memory deficits in maze tasks; enhanced LTP; genetic linkage in man to restless legs syndrome and ADHD.	Self, NGL-3, IL1RAcP#, IL1RAPL1, SLTRK3 †	Liprin-α	[24, 26, 60, 63, 64, 67-69, 86, 87, 99, 100]
PTPσ	*Chick, rodent, Xenopus*	*chick*	rodent		HSPG, CSPG, NGL-3 , SLTRK1,2,4-6†, IL1RAcP, NUCLEOLIN, TRKC	TRKs, RAC GTPase activity through p250GAP, Liprin-α	[24, 25, 48-51, 60, 67, 69, 71, 100-102]
LAR	*rodent, Xenopus*		rodent	Spatial learning deficits and increased nocturnal activity	Self, NGL-3, IL1RAcP	Liprin-α TRKB	[52, 53, 55, 60, 62, 69, 72, 88, 100]
PTPRO	Chick, *rodent*	*chick*		Nociceptive deficits			[24, 28, 83]

Text in *italics* indicates where in vivo evidence is documented

* Ligands with likely physiological relevance; other in vitro interactions are seen [57]

† inhibitory synapse for PTPδ ; excitatory synapse for PTPσ

¶ non-cell autonomous action on neurons, through either PTPζ expression on glia, or phosphacan

\# PTPδ binds more strongly to IL1RacP than PTPσ or LAR (ref [69])

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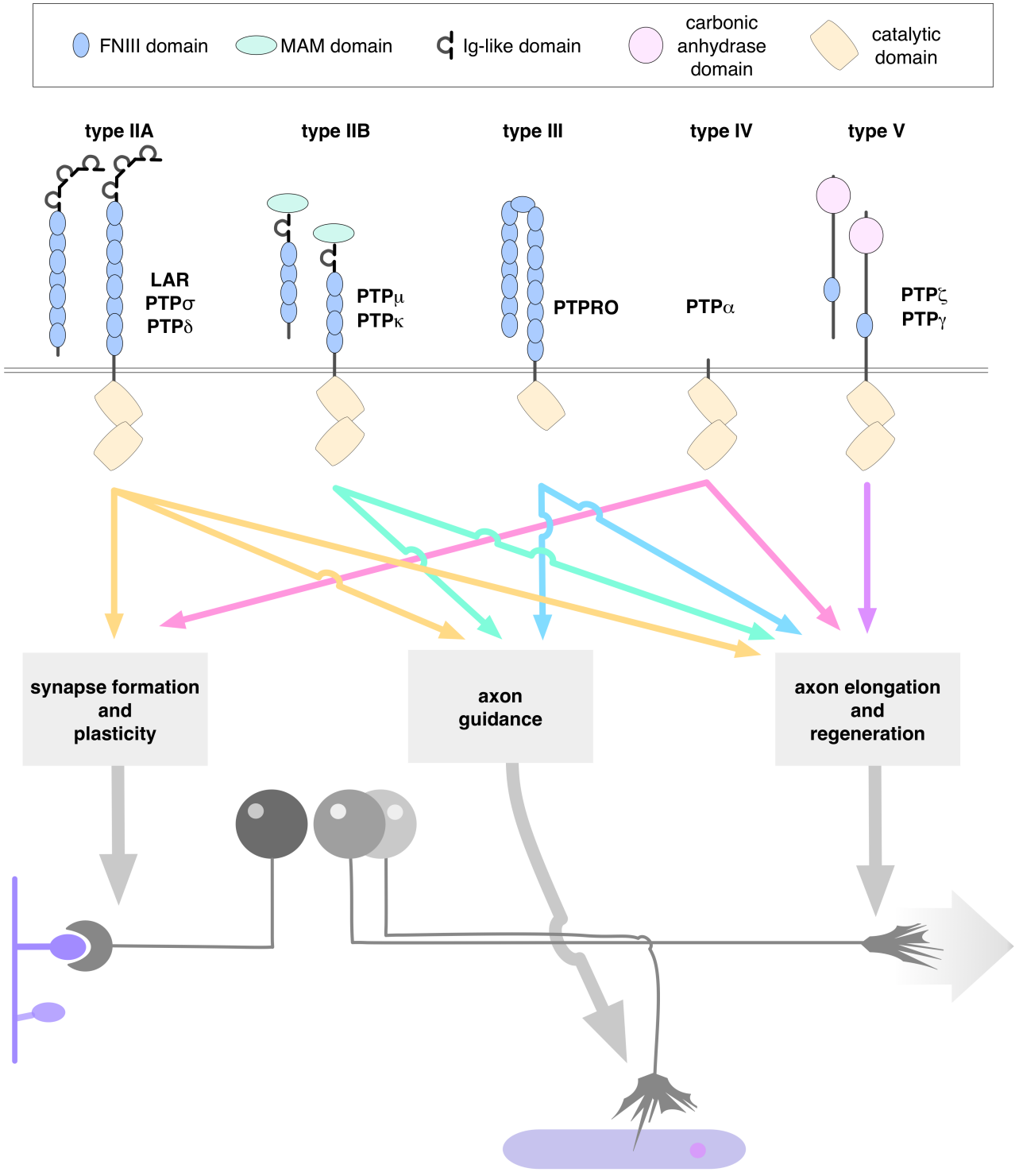

Figure 1
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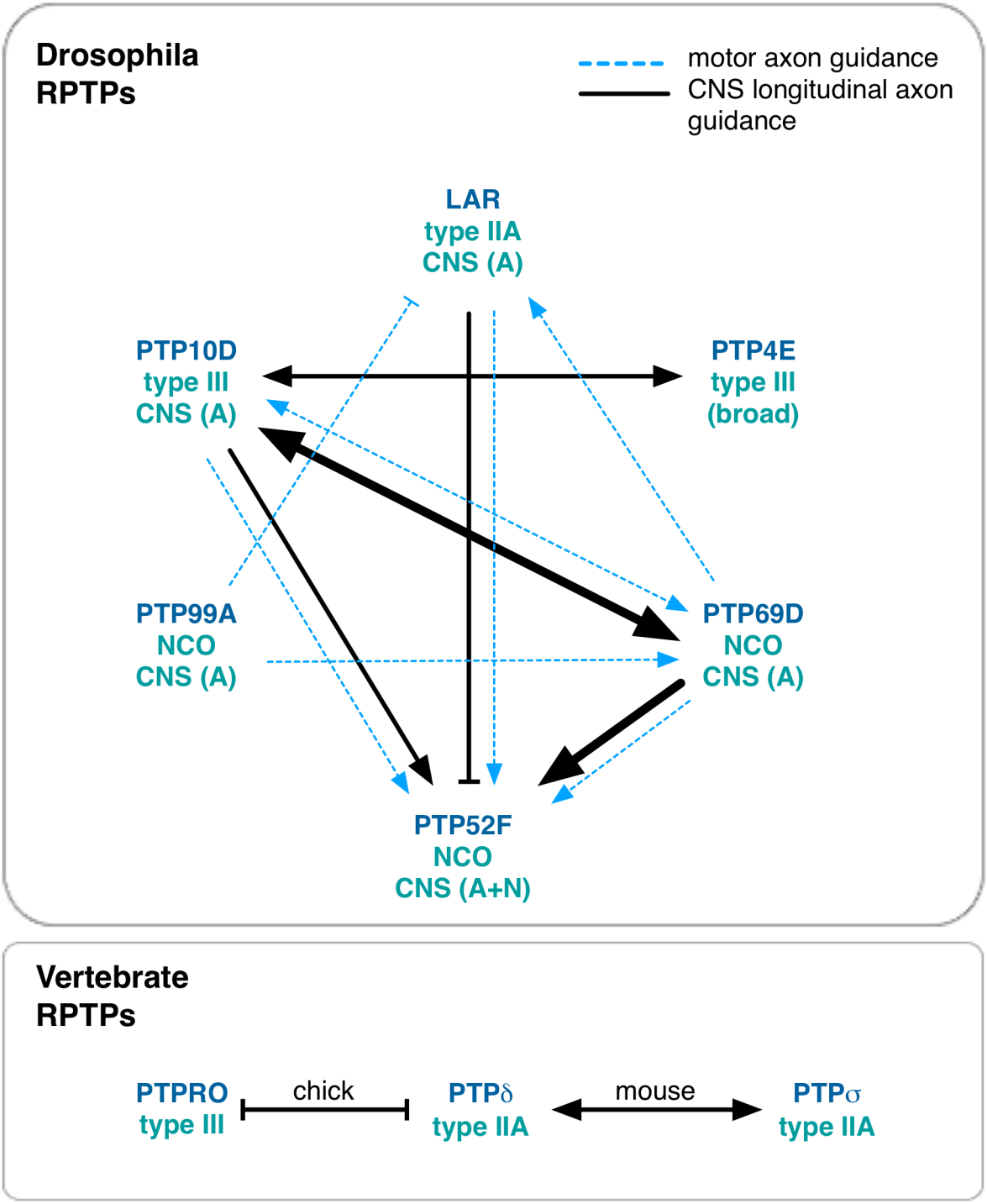

Figure 2
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