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Review

The many roles of PTK7: A versatile regulator of cell–cell communication

Hanna Peradziryi [a], Nicholas S. Tolwinski [b], Annette Borchers [a,*]

[a] Department of Developmental Biochemistry, Center for Molecular Physiology of the Brain (CMPB), GZMB, University of Göttingen, Justus-von-Liebig-Weg 11, 37077 Göttingen, Germany

[b] Department of Molecular, Cellular and Developmental Biology, University of Michigan, Ann Arbor, MI 48109-1048, USA

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ABSTRACT

PTK7 (protein tyrosine kinase 7) is an evolutionarily conserved transmembrane receptor with functions in various processes ranging from embryonic morphogenesis to epidermal wound repair. Here, we review recent findings indicating that PTK7 is a versatile co-receptor that functions as a molecular switch in Wnt, Semaphorin/Plexin and VEGF signaling pathways. We focus in particular on the role of PTK7 in Wnt signaling, as recent data indicate that PTK7 acts as a Wnt co-receptor, which activates the planar cell polarity pathway, but inhibits canonical Wnt signaling.

Introduction

Cell–cell communication coordinates complex cell movements in embryogenesis as well as adult tissue homeostasis. During embryonic development cell divisions start the generation of a multicellular organism, and are followed by a series of complex and coordinated cell movements necessary for embryonic patterning and organ formation. Collectively, these morphogenetic movements change the shape and form of differentiating tissues through such processes as gastrulation, the closure of the neural tube, and the migration of neural crest cells. In adult organisms coordinated cell movements are relevant for wound healing and regeneration. In order to ensure precise regulation of these processes individual cells have to communicate with each other. To accomplish this, cells send out cues providing positional information that receiving cells translate into cellular asymmetries and directed locomotion. These molecular cues include members of the Wnt family of secreted glycoproteins, which are able to activate a broad range of downstream signaling events depending on cellular context [2,54,61,62,68,94]. Thus, receiving cells need mechanisms to favor specific signaling outcomes allowing for distinct cellular responses. One way that this can be achieved is by using specific receptor complexes to detect and subsequently respond to distinct signals.

One such molecular switch, PTK7 (protein tyrosine kinase 7)[1] is a transmembrane receptor that regulates morphogenetic processes. Identified in colon carcinoma cells and named colon carcinoma kinase-4 (CCK-4) [63], PTK7 was later shown to be required for morphogenetic cell movements during embryonic development. Orthologs of PTK7 include Hydra Lemon, *Drosophila* off-track (otk), chicken kinase-like gene (KLG) and mouse PTK7 [64]. Functions in embryonic morphogenesis range from axon guidance in *Drosophila* [11,75,107] to the regulation of gastrulation, neural tube closure, neural crest migration and cardiac morphogenesis in vertebrates [53,84,92,110]. In addition PTK7 is also required for epidermal wound repair and its expression is frequently deregulated in cancer [4,10,27,28,31,63,65,74]. Considering its critical role in morphogenetic processes the elucidation of the signaling mechanism of PTK7 is a topic of intense ongoing research. This review describes recent progress in the understanding of PTK7 signaling with a focus on its potential function as a molecular switch between signaling pathways.

PTK7 is a Wnt co-receptor involved in the choice of Wnt signaling outcome

Recently, we described PTK7/Otk as a novel Wnt co-receptor that confers specificity in response to Wnt ligands [71]. Wnt signaling pathways are evolutionarily conserved and regulate numerous aspects of embryogenesis and maintenance of adult tissue homeostasis [18,52,54,61,72]. The basic mechanism of the Wnt signaling pathway begins with the Frizzled receptor binding the extracellular Wnt ligand. In absence of Wnts, the destruction-complex consisting of APC, Axin, glycogen synthase kinase 3 (GSK3) and casein kinase 1 (CK1) promotes proteasomal degradation of the transcriptional

* Corresponding author.
E-mail address: annette.borchers@gmail.com (A. Borchers).

[1] *Abbreviations used:* PTK7, protein tyrosine kinase 7; CCK-4, colon carcinoma kinase-4; otk, off-track; KLG, kinase-like gene; GSK3, glycogen synthase kinase 3; CK1, casein kinase 1; PCP, planar cell polarity; Dsh, Disheveled; vangl2, VanGogh; RACK1, receptor of activated protein kinase C; MMP, matrix metalloproteinase; chz, chuzhoi; VEGFR2, vascular endothelial growth factor receptor type 2; FAK, focal adhesion kinase.

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activator β-catenin. Wnt binding results in inhibition of the destruction complex and stabilization of β-catenin, which subsequently translocates to the nucleus activating β-catenin-responsive genes. In addition to this canonical Wnt signaling pathway, which regulates cell proliferation and differentiation, alternative, β-catenin-independent, non-canonical Wnt signaling pathways have been identified. These non-canonical Wnt signaling pathways control cellular polarity and cell movement and signal for example via small GTPases of the Rho family resulting in modification of the cytoskeleton [81]. Which pathway is activated is at least in part determined by the choice of Frizzled co-receptor [2,93,94,96]. For example, Wnt5a and Wnt11, known regulators of non-canonical Wnt signaling, can induce canonical Wnt signaling depending on receptor context [15,40,58,89]. Frizzled co-receptors like LRP5/6 or Arrow activate canonical Wnt signaling while co-receptors such as Ror, Derailed and Ryk regulate non-canonical signaling [8,35,36,41,73,80,88,93,104,111]. PTK7 now joins this list of Wnt co-receptors required for pathway selectivity.

PTK7 regulates planar cell polarity

Recent functional analysis points to a role for PTK7 as a Wnt co-receptor in the non-canonical Wnt signaling pathway determining planar cell polarity (PCP). During development many epithelial tissues and organs acquire a polarity orthogonal to their apical–basal axis, which is referred to as PCP. The signaling pathway that determines PCP was discovered in *Drosophila*, where it controls the uniform orientation of wing hairs, ommatidial rotations, and bristles on the body [1,37,48]. *Drosophila* PCP genes were identified by their loss of function phenotypes displaying irregular hair orientation and were accordingly named *frizzled* or *disheveled*. Subsequently these genes were shown to be part of a non-canonical, β-catenin-independent, Wnt signaling pathway. This core PCP pathway is evolutionarily conserved and contains components like the transmembrane proteins Frizzled, Strabismus/VanGogh, Flamingo/Celsr and the intracellular regulators Disheveled (Dsh), and Prickle [34,57,61,82,97]. Knockouts of the mouse orthologs of these genes lead to polarity defects of inner ear sensory cells and a severe neural tube closure defect [22,39,66,101,102]. Interestingly, PTK7 mutant mice showed identical phenotypes and genetic interaction with *vangl2* (VanGogh), indicating that PTK7 plays a role in the regulation of vertebrate PCP [53].

PTK7 function is required for a broad range of processes regulated by the PCP signaling pathway. Convergent extension is one such process, and defects in it are considered to be a hallmark of impaired vertebrate PCP signaling [78]. Convergent extension describes a morphogenetic cell movement required for gastrulation and neural tube closure [99]. Recent data showed that PTK7 is necessary for convergent extension cell movements in *Xenopus*, zebrafish and mice [33,103,110] indicating a conserved role in this process. PTK7 is further required for neural crest migration, another PCP signaling regulated process. Neural crest cells are a pluripotent population of highly migratory cells, which contribute to a wide range of vertebrate tissues and organs including craniofacial structures. Pioneering work from Roberto Mayor's laboratory has shown that PCP signaling is required for neural crest migration and regulates cell polarity and directionality of migrating neural crest cells [14,24]. Inhibition of PCP factors like Fz7, Dsh and Wnt11 in *Xenopus* embryos blocks neural crest migration [24]. Interestingly, we observe the same phenotype if PTK7 is knocked down [84]. Overall, these studies confirm a role for PTK7 in various PCP-controlled aspects of vertebrate development.

The polarity role of Otk in *Drosophila* is more complex. The current data suggest that PTK7 regulates vertebrate PCP, but the *Drosophila* ortholog of PTK7, Otk, is not required for PCP signaling. RNAi knockdowns and mutant *otk* clones did not show wing hair defects. However, overexpression of Otk led to defects in wing hair polarity, indicating that Otk can affect PCP in *Drosophila* [71]. Additionally, Wnts have been excluded from PCP signaling in *Drosophila*, whereas Otk functions as a co-receptor for Wnt4 [71,95]. It is, however, possible that Otk does have a role in non-canonical Wnt signaling that is not the same as the PCP pathway in fly wings. There are several non-canonical pathways that affect cell polarity and motility [81]. In *Drosophila* these pathways are poorly understood, but the effects of Otk and Wnt4 correlate with morphogenetic cell rearrangements in the late embryo that are regulated by PCP and novel polarity mechanisms [19,26,45,46,77,85]. Here Wnt pathway components interact with polarity proteins generating cellular asymmetries and regulating the proper arrangement of epidermal structures. Further investigations will be required to determine what role Otk/Wnt4 plays in this process.

In addition to functions in embryonic PCP signaling, PTK7 may also be required for adult PCP-dependent processes. For example a role in wound healing is suggested by the observation that PTK7 and other core PCP proteins, like Vangl2, Celsr1, Scrb1, regulate epidermal wound repair [10]. PTK7, therefore, plays a role in a broad range of processes regulated by PCP signaling. However, it is unclear how it intersects with the PCP signaling pathway, and if its molecular signaling mechanism is conserved in different tissues and organisms.

PTK7 functions by recruiting Dsh

The PTK7 downstream signaling is still largely unknown, but we recently showed that PTK7 functions by recruiting Dsh to the plasma membrane (Fig. 1A). Dsh is a key regulator of canonical (β-catenin-dependent) and non-canonical Wnt signaling pathways holding a position at the branching point of different pathways [29]. The protein consists of three major domains: the DIX, PDZ and DEP domain. Signaling via the DIX domain has been attributed to canonical Wnt signaling, while the DEP domain has been implicated in PCP signaling; the PDZ domain is shared by both pathways [7,38,42,79]. As Dsh occupies a key position at the intersection of different Wnt signaling pathways, pathway specificity may also depend on distinct interaction partners and subcellular localization of Dsh [29,105]. For example membrane localization of Dsh is a prerequisite for activation of vertebrate PCP signaling [69]. Interestingly, we find that PTK7 is able to recruit Dsh to the plasma membrane [84], suggesting that it activates PCP signaling by affecting Dsh localization.

How is the PTK7-mediated Dsh recruitment accomplished? According to its amino acid sequence PTK7 is a transmembrane protein with extracellular immunoglobulin domains and an intracellular tyrosine kinase homology domain. The kinase homology domain is evolutionary conserved, but lacks amino acid motifs critical for catalytic activity [47,59]. Kinase activity could not be demonstrated for the hydra, chicken, mouse and human orthologs [17,44,59,63]. In *Xenopus* the kinase domain functions to translocate Dsh to the plasma membrane; however, deletion of the kinase domain of PTK7 or the PDZ domain of Dsh abolishes this function [84]. The PTK7–Dsh interaction is mediated by RACK1 (receptor of activated protein kinase C) [103], an evolutionary conserved adapter protein, which was first identified as a receptor of activated protein kinase C [60]. Our data suggest that RACK1 is recruited to the plasma membrane via the kinase domain of PTK7 and thereby assists in the membrane localization of Dsh (Fig. 1A). RACK1 likely contributes to Dsh recruitment by interaction with PKCδ1 [103], but it remains unclear if PKCδ1 affects Dsh localization simply by mediating protein binding or by mechanisms involving its kinase activity. Interestingly, Ping Cheng's laboratory recently identified RACK1 as an interaction partner of Vangl2, required for Vangl2 membrane local-

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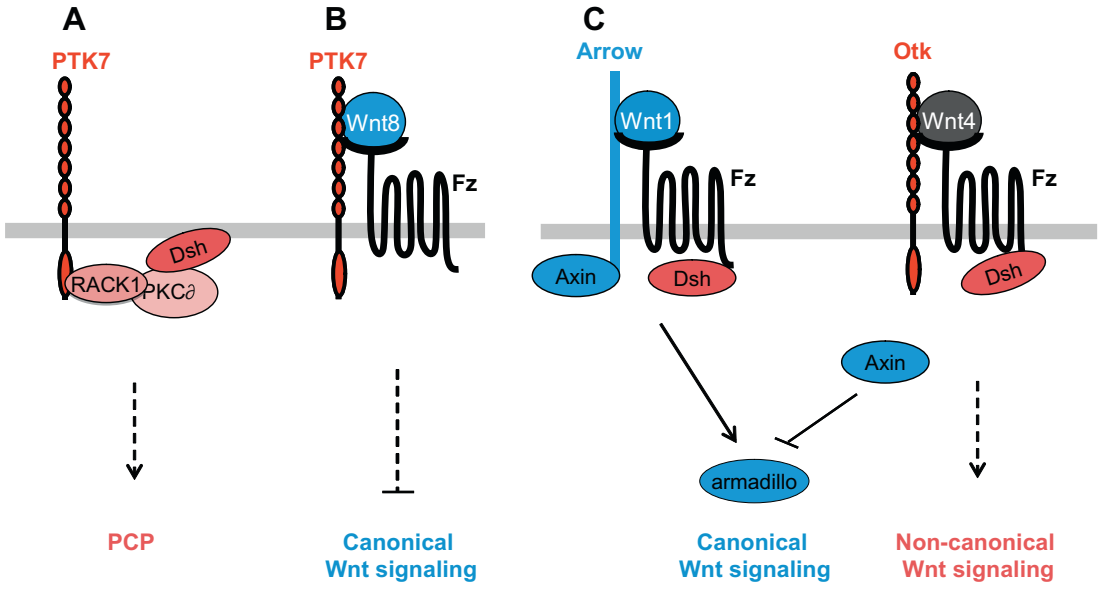

Fig. 1. PTK7 activates non-canonical Wnt signaling, but inhibits canonical Wnt signaling. (A) In *Xenopus*, PTK7 activates PCP signaling by recruiting Dsh to the plasma membrane. The PTK7–Dsh interaction is mediated by RACK1, which contributes to Dsh recruitment by interaction with PKCδ1. (B) In addition, vertebrate PTK7 functions as a Fz co-receptor and interacts with canonical members of the Wnt family to inhibit canonical Wnt signaling, possibly by trapping canonical Wnt ligands in a PCP signaling complex. (C) In *Drosophila* Wnt1 activates canonical Wnt signaling by interacting with a Fz/Arrow co-receptor complex, which recruits Axin and Dsh. Axin recruitment leads to disassembly of the destruction complex thereby preventing the degradation of the β-catenin ortholog Armadillo. The PTK7/Otk co-receptor is specific for Wnt4 and recruits Dsh but not Axin to the plasma membrane. Thus, cytoplasmic Axin can contribute to Armadillo degradation and inhibition of canonical Wnt signaling, while membrane-localized Dsh can participate in the activation of non-canonical Wnt signaling.

ization [51]. The authors find that RACK1 plays a role in cell polarization, oriented cell division and convergent extension in zebrafish supporting a role in PCP signaling. It will be interesting to see if PTK7 and Vangl2 signaling compete for RACK1 interaction or if their downstream signaling pathways converge at the level of RACK1.

The first step of PTK7 signaling is Dsh recruitment to the plasma membrane, but the downstream signaling events remain elusive. A general problem in PCP signaling is that loss of function phenotypes cannot distinguish between an activating or inhibiting function, as both scenarios can for example result in failure of convergent extension thereby generating identical phenotypes [100]. However, as PTK7 promotes Dsh membrane localization, which has been attributed to activation of PCP signaling, it likely functions as an activator of PCP. This is further supported by the finding that overexpression of PTK7 leads to nuclear localization of phosphorylated JNK [84], indicating activation of downstream PCP signaling. Further, using an ATF2-based luciferase reporter to monitor activation of non-canonical Wnt signaling, we find evidence that PTK7 activates PCP signaling in *Xenopus* [71]. Taken together these phenotypic as well as mechanistic data support a role of PTK7 in the activation of PCP signaling.

PTK7 affects canonical Wnt signaling

PTK7 function is likely not limited to PCP signaling but can extend to canonical Wnt signaling as well. Recently, PTK7 was shown to interact with key players of canonical Wnt signaling including β-catenin [76], canonical Wnt proteins and Frizzled7 [71] (Fig. 1B), but the role of PTK7 in canonical Wnt signaling remains controversial. The laboratories of Borg and Kodjabachian propose a model in which PTK7 functions in the activation of canonical Wnt signaling by stabilizing β-catenin. They find that PTK7 interacts with β-catenin and is required for β-catenin-dependent transcriptional activity in mammalian cells and *Xenopus* embryos. Further, they observe that knockdown of PTK7 in *Xenopus* embryos inhibits the induction of the Spemann's organizer, which relies on β-catenin signaling [76]. However, our data contradict these findings. In our hands PTK7/Otk inhibits canonical Wnt signaling in functional assays using *Xenopus*, *Drosophila* or mammalian cells [71]. Further, loss of function of PTK7 activates canonical Wnt signaling in *Xenopus* and mammalian reporter assays. Moreover, we do not observe significant defects in *Xenopus* organizer gene expression compared to control embryos (unpublished observations). Thus, we propose that PTK7 inhibits canonical Wnt signaling, but the molecular mechanism remains unknown.

PTK7 is selective in the Wnt family members that it interacts with. In *Xenopus*, PTK7 interacts with Wnt3a and Wnt8 (activators of canonical Wnt signaling), and this interaction requires the presence of Fz7, suggesting that PTK7 is a Frizzled co-receptor [71] (Fig. 1B). Whether Wnt binding to PTK7 leads to post-translational modification of the PTK7 co-receptor is currently unclear, although an attractive possibility given the use of phosphorylation in LRP5/6 activation [23,112]. However, PTK7-mediated Dsh recruitment is apparently independent of Wnt binding. First, co-expression of Wnt ligands does not prevent Dsh recruitment (our unpublished results). Second, a PTK7 construct lacking the extracellular domain required for Wnt binding is able to recruit RACK1 [103]. Furthermore, although PTK7 seems to activate PCP signaling via interaction with Dsh, this interaction is dispensable for inhibition of canonical Wnt signaling. A PTK7 construct unable to recruit Dsh, can still inhibit canonical Wnt signaling. Thus, the specific mechanism of how PTK7 affects canonical signaling remains to be investigated. Interestingly, while PTK7 interacts with canonical Wnt3a and Wnt8, it does not appear to interact with non-canonical Wnt5a or Wnt11 [71]. Hence, we hypothesize that PTK7 traps canonical Wnts in a non-canonical receptor complex thereby preventing them from activating canonical Wnt signaling. One possibility is that PTK7 competes for Fz binding with another co-receptor involved in the activation of canonical Wnt signaling like LRP6. When a PTK7/Fz complex is formed, Fz binding to LRP6 could be reduced and canonical Wnt signaling cannot be activated efficiently.

Another possibility is that the PTK7/Fz Wnt-receptor complex fails to inhibit β-catenin degradation. In *Drosophila*, Otk binds to Dsh but not to Axin [71] (Fig. 1C). In contrast to Dsh, which is involved in both canonical and PCP signaling, Axin is only involved in canonical signaling. Axin is a key regulator of the canonical Wnt pathway through its assembly of the destruction complex that prevents β-catenin from accumulating and entering the nucleus [49,90,91]. Axin recruitment to the membrane by LRP5/6 is a key activating step for the canonical signaling pathway [56]. Wnt binding to a Otk/Fz complex, therefore, does not recruit Axin to the membrane, and the *Drosophila* β-catenin ortholog Armadillo is degraded (Fig. 1C). In this context the binding of β-catenin to PTK7 is an intriguing finding [76]. Generally, recruitment of β-catenin to the membrane is associated with its adhesive functions, as under normal conditions release of the membrane fraction has little effect on nuclear signaling due to the effectiveness of the destruction complex [52]. One possibility is that PTK7 is involved in the asymmetric distribution of β-catenin at the membrane. In fly embryos, junctions become asymmetric during morphogenetic events [5,19]. Our unpublished observations suggest that Otk is also asymmetrically distributed during morphogenesis suggesting a possible link between these processes. Future research will have to clarify the molecular mechanism by which PTK7/Otk affects canonical Wnt signaling.

PTK7 is a matrix metalloproteinase target

PTK7 has recently been shown to be a matrix metalloproteinase (MMP) target adding yet another level of complexity to PTK7 signaling. PTK7 is a target of membrane type-1 matrix metalloproteinase (MT1-MMP/MMP14), a membrane-anchored proinvasive and promigratory MMP controlling cell adhesion and migration [3,9,108]. MT1-MMP cleaves full-length PTK7 in the seventh immunoglobulin domain thereby generating a secreted extracellular fragment of PTK7. Inhibition of MT1-MMP proteolysis in zebrafish resulted in similar convergent extension defects as loss of PTK7 and genetic interaction of MT1-MMP and PTK7 was observed [21,33]. These findings suggest that MT1-MMP mediated proteolysis of PTK7 is required for PCP-regulated processes like convergent extension. This hypothesis is further supported by the identification of a novel mouse PCP mutant *chuzhoi* (*chz*), which carries a splice site mutation in the *ptk7* gene [70]. *Chz* mice show typical PCP defects like open neural tube, shortened anterior–posterior body axis or misoriented inner ear hair cells. The *chz* mutation leads to an insertion of three additional amino acids (Ala-Asn-Pro) between the fifth and the sixth extracellular immunoglobulin domains of PTK7 [70]. This insertion results in the formation of an additional MT1-MMP cleavage site in the PTK7 protein leading to aberrant PTK7 proteolysis and changes in cell migration behavior [32]. Thus, MT1-MMP-mediated proteolysis can generate soluble PTK7 fragments and excessive proteolysis, like in the *chz* mutants, may cause PCP defects. Previously, the soluble PTK7 ectodomain has been shown to lead to similar defects as loss of PTK7 in the regulation of angiogenesis [83], however, its mechanistic implications are unclear. Potentially it could prevent homotypic interaction of PTK7 [53,75] or affect the formation of Wnt receptor complexes, thereby adding further complexity to the PTK7 "signaling switch". In this context it is also interesting to note that different splice variants of PTK7 were identified in human testis; one lacking most of the seventh Ig domain, where the MT1-MMP cleavage side resides. Splice variants of PTK7 are differentially expressed suggesting that alternative splicing may contribute to cell-type specific signaling functions [43]. Future research will have to follow up on these interesting leads.

PTK7 functions as Plexin or VEGFR co-receptor

PTK7's function as a molecular switch between different signaling pathways is likely not limited to Wnt signaling. In addition to being a Wnt co-receptor, PTK7/Otk can also form a complex with proteins of the Plexin protein family. Originally discovered as regulators of axon guidance, Plexins are transmembrane molecules that transduce signals from ligands of the Semaphorin family leading to cytoskeleton reorganization thereby affecting cell shape, motility and cell–cell interaction [20,86,87,106]. Semaphorins and Plexins were later acknowledged as broad regulators of cell–cell communication with functions in embryogenesis and adult tissue homeostasis. They are important for the formation of the cardiovascular, endocrine and immune systems, regulate neural crest migration and have also been implicated in tumorigenesis [13,30,67]. Depending on receptor context Semaphorins can function as chemorepellents or attractants [25]. For example, the presence of the neuropilin-1 co-receptor can distinguish if Sema3E/PlexinD1 signaling leads to axon repulsion or attraction [16]. Thus, like in the Wnt signaling pathway receptor context may determine downstream signaling in response to a specific Semaphorin.

PTK7/Otk could have a conserved role as a molecular switch in Plexin/Semaphorin signaling. In *Drosophila*, Otk forms a complex with PlexinA1 that mediates repulsive axon guidance in response to Sema1A [107]. The phenotype and molecular interaction of PTK7 with PlexinA1 is also conserved in vertebrates. In *Xenopus* PTK7 cooperates with PlexinA1 to affect migration of cranial neural crest cells [98]. In chick KLG/Otk is a PlexinA1 co-receptor affecting the signaling response to Sema6D. In different regions of the chick cardiac tube the PlexinA1/Sema6D complex mediates two distinct biological functions, promoting cell migration in the conotruncal segment and inhibiting it in the ventricular segment of the heart. Toyofuku and colleagues showed that PlexinA1 forms a complex with Otk in the heart ventricle segment to mediate the inhibitory effect of Sema6D on cell migration. On the other hand, in the conotruncal segment PlexinA1 forms a receptor complex together with VEGFR2 (vascular endothelial growth factor receptor type 2) to promote cell migration in response to the same ligand, Sema6D [92] (Fig. 2A). Thus, in the developing chick heart, PTK7 and VEGFR2 co-receptors enable PlexinA to have distinct biological activities in adjacent regions.

While there is strong evidence that PTK7/Otk cooperates with Plexin, it is still unknown how PTK7 affects downstream Plexin signaling. Plexins themselves lack kinase activity but can become tyrosine phosphorylated [55,87]. As PTK7 also lacks kinase activity, PTK7/Plexin could signal by recruiting a catalytically active kinase to the receptor complex. A similar signaling mechanism has been reported for Ryk/Derailed, another member of the receptor tyrosine family that lacks kinase activity and functions in axon guidance [6,12]. SRC64B, a Src family non-receptor tyrosine kinase, is important for Derailed signaling in the central nervous system of *Drosophila* embryos [109]. Derailed and SRC64B interact with each other resulting in Derailed phosphorylation and increased SRC64B activity [109]. It is possible that upon binding to the Plexin/Semaphorin complex PTK7 recruits an as yet unidentified kinase that might phosphorylate Plexins to transduce the signal. Further studies are needed to clarify the signaling mechanism of PTK7 as a component of the Plexin receptor complex.

The role of PTK7 as a co-receptor regulating various dynamic cellular processes is further supported by the identification of its interaction with Flt-1 (VEGFR1, vascular endothelial growth factor receptor 1), a receptor important for angiogenesis control [50]. A role of PTK7 in angiogenesis was first reported by Shin and colleagues, who showed that PTK7 is expressed in vascular endothelial cells and is required for cell migration and tube formation

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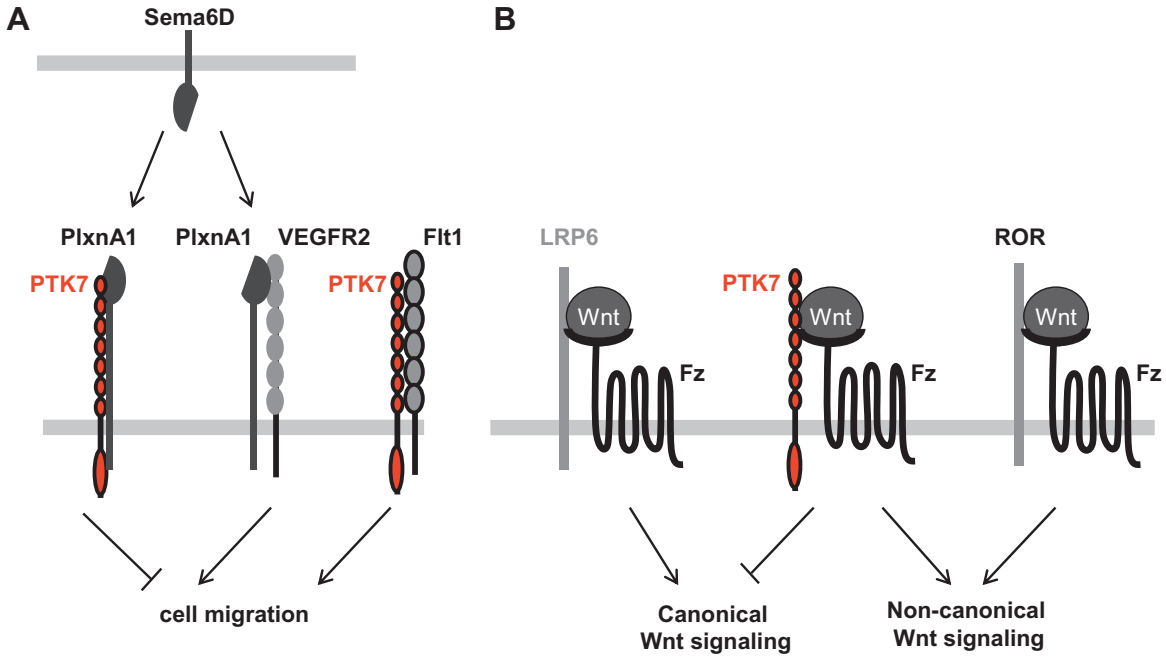

Fig. 2. PTK7/Otk is a versatile co-receptor that functions as a molecular switch in Wnt, Semaphorin/Plexin and VEGF signaling pathways. (A) PTK7/Otk functions as a co-receptor in Plexin and VEGF signaling pathways. During chick cardiac morphogenesis PlexinA1 (PlxnA1) forms a complex with Otk or with VEGFR2 to inhibit or activate cell migration in response to Sema6D. Additionally, human PTK7 can form a complex with Flt-1 (VEGFR1) to promote endothelial cell migration and tube formation during angiogenesis. (B) The choice between canonical and PCP Wnt pathways is determined by the presence of Fz co-receptors. LRP6 activates the canonical Wnt pathway while PTK7 and Ror activate non-canonical Wnt pathways.

during angiogenesis [83]. Later PTK7 was shown to interact specifically with Flt-1 (VEGFR1) but not with Flk-1 (VEGFR2). Additionally, the authors demonstrated that PTK7 is required for VEGF-induced Flt-1 phosphorylation and followed by downstream events like phosphorylation of focal adhesion kinase (FAK) and Akt [50]. Hence, PTK7 seems to be an essential Flt-1 co-receptor required for endothelial cell migration and tube formation during angiogenesis [50,83] (Fig. 2A).

These data demonstrate that PTK7 is a versatile co-receptor for Wnt, Semaphorin and VEGF signaling and support a role of PTK7 as a molecular switch between signaling pathways (Fig. 2A and B). In Wnt and Semaphorin signaling the presence of the PTK7 co-receptor can determine the signaling outcome. If the formation of these co-receptor complexes is the result of the spatial–temporal expression pattern of PTK7 or dynamically regulated by the presence of specific ligands is currently an unresolved issue.

Conclusions

To initiate specific signaling cascades cells detect differences between presented ligands, and activate one downstream response and not another. In Wnt signaling, there are several Wnt ligands and different downstream pathways, however it is unclear how cells distinguish between Wnt molecules. One solution to this problem was suggested by the discovery that discrete Wnt-co-receptor modules activate distinct Wnt signaling pathways. This led to a model where recruitment of different co-receptors upon binding Wnt ligands activates distinct intracellular pathways by engaging different signaling molecules [94]. We have proposed that PTK7/Otk is exactly this type of Wnt co-receptor in both *Drosophila* and vertebrates (Fig. 1). As many of the upstream components of both canonical and non-canonical signaling pathways are the same (for example Frizzled and Disheveled), the presence of a distinct co-receptor may be the deciding factor as to which pathway is activated. It is tempting to speculate that the presence of PTK7, Ryk or Ror in a Wnt bound complex determines which downstream effectors are recruited to the membrane deciding which pathway will be activated (Fig. 2B). This system would provide a simple switch, likely depending on cell type and which Wnt was present, to determine cellular outcomes. It is likely that since PTK7/Otk is also a co-receptor for VEGF and Semaphorin signals, its function as a signaling switch is not limited to Wnt signaling (Fig. 2A). Although progress has been made in placing PTK7 in the cellular signaling network many questions remain whose answers may help us gain a better understanding of cell–cell communication.

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