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Eye Defects in Receptor Protein-Tyrosine Phosphatase α Knock-Down Zebrafish

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ABSTRACT **Receptor protein-tyrosine phosphatase alpha (RPTPα) is highly expressed in the developing retina of different species, but little is known about its function there. Here, we report that injection of antisense morpholinos in zebrafish embryos reduced RPTPα expression to almost nondetectable levels up to 3 days postfertilization (dpf). RPTPα was detectable again from 4 dpf onward. RPTPα knock-down resulted in smaller eyes. Examination of sections of the retina at different developmental stages demonstrated that already at 28 hours postfertilization (hpf) fewer cells were present in the retina of RPTPα-morpholino–injected embryos. At 3 dpf, the layered organization of the retina was absent. In addition, the morphology and labeling with an axon specific antibody, acetylated tubulin, demonstrated that most cells appeared to be undifferentiated. Strikingly, at 5 dpf the lamination of the retina was partially restored, concomitant with re-expression of RPTPα protein. Although cells in the retina were now differentiated, the layering of the retina remained disrupted and significant gaps were observed in the amacrine cell layer. Therefore, knock-down of RPTPα protein provides evidence that RPTPα is essential for normal retinal development.**

Key words: protein-tyrosine phosphatase; eye development; retinal lamination; morpholino; knock-down

INTRODUCTION

The development of the vertebrate eye and the zebrafish eye in particular has been characterized in considerable detail (Cajal, 1893; Dowling, 1987; Larison et al., 1990; Schmitt and Dowling, 1994; Raymond et al., 1995; Passini et al., 1997; Hu and Easter, 1999). The retina is a highly organized structure and is divided into three major cellular layers, the outer nuclear cell layer (ONL), the inner nuclear cell layer (INL), and the ganglion cell layer (GCL) (reviewed in Dowling, 1987). The inner- (IPL) and the outer (OPL) plexiform layers separate the three nuclear layers. The retinal layers consist of seven different cell types. Six of these are neuronal, whereas one is glial (the Müller cells). Birthdating studies have shown that each of the seven retinal cell types is generated from multipotent progenitor cells at strictly defined times during development (Turner and Cepko, 1987; Holt et al., 1988; Turner et al., 1990). Before the appearance of postmitotic cells, the retina consists of a single neuroepithelial sheet composed of elongated undifferentiated cells. Retinal neurogenesis occurs in a stereotypical spatiotemporal manner and is characterized by differentiation of precursor cells into neurons and glia. The first cells to exit the cell cycle are retinal ganglion cells that establish the innermost layer of the retina followed by waves of neurogenesis that form the inner nuclear layer and the outer nuclear layer (Malicki, 2000). The molecular mechanisms underlying retinal differentiation and the establishment of lamination are far from clear.

Protein phosphorylation on tyrosine residues is an important cell signalling mechanism that plays a pivotal role in cell proliferation, differentiation, and migration. Cellular phosphotyrosine levels are regulated by the protein-tyrosine kinases (PTKs) and protein-tyrosine phosphatases (PTPs). Recent work has provided insights into the role of PTPs in development. Several PTPs play a crucial role in embryogenesis (Van Vactor, 1998; den Hertog, 1999; Stoker, 2001). The transmembrane PTPs, tentatively called receptor PTPs (RPTPs) may play an important role in eye development, because several members of this subfamily of RPTPs are highly expressed in the developing eye of several vertebrate species. For instance, the three LAR subfamily members, i.e., LAR, PTPδ, and Crypα, are expressed in overlapping but distinct patterns in the developing *Xenopus* retina (Johnson and Holt, 2000). Similarly, five different RPTPs were found to have different but overlapping expression patterns in the developing chick retina (Ledig et al., 1999). One of these RPTPs is RPTPα, a typical RPTP. RPTPα expression was first found throughout the neuroepithelium of the developing eye (chick E6), then it becomes restricted to Muller cells (chick E10), and later is expressed in amacrine cells as well (E14) (Ledig et al., 1999). Whereas RPTPα is expressed in the developing mouse eye (den Hertog et al., 1996), little is known about the function of RPTPα in vivo. RPTPα gene ablation studies have been reported (Ponniah et al., 1999; Su et al., 1999), but did not provide insight into the role of RPTPα in mouse development. Here, we demon-

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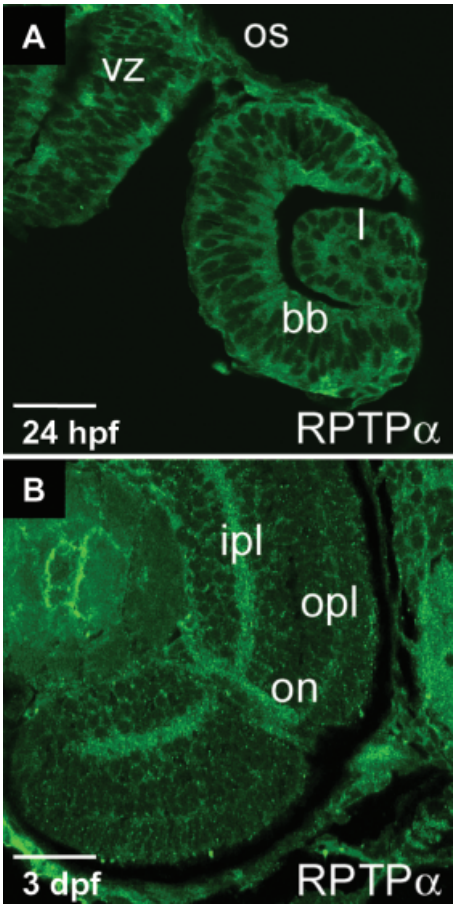

Fig. 1. Expression of receptor protein-tyrosine phosphatase alpha (RPTPα) in the zebrafish eye. Indirect immunofluorescence, by using affinity purified anti-RPTPα antibody (AP5478) of a 24 hours postfertilization (hpf) embryo (**A**) and a 3 days postfertilization (dpf) embryo (**B**). Close-up photomicrographs of the eye are shown. bb, basal border; ipl, inner plexiform layer; on, optic nerve; opl, outer plexiform layer; os, optic stalk; l, lens; vz, ventricular zone. Scale bars = 150 μm in A, 40 μm in B.

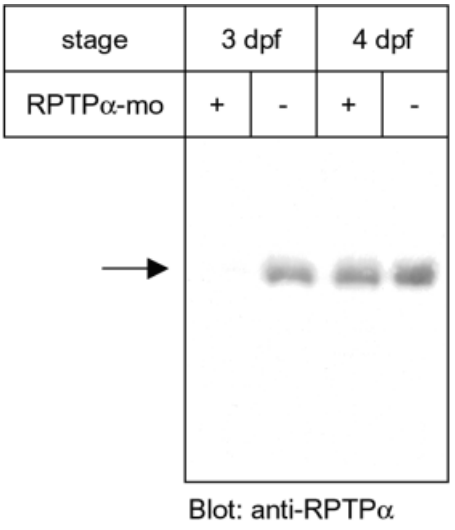

Fig. 2. Transient knock-down of receptor protein-tyrosine phosphatase alpha (RPTPα) protein expression. A total of 0.5 ng of RPTPα-morpholino (-mo) was injected at the one-cell stage, and injected (+) or noninjected (-) embryos were collected at 3 days postfertilization (dpf) or 4 dpf, lysed, and loaded onto a 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis gel. The gel was blotted, and the blot was probed with an affinity-purified anti-RPTPα antibody. The blot was developed by using enhanced chemiluminescence. zf-RPTPα is indicated with an arrow.

strate that RPTPα is expressed in the developing zebrafish eye, and by using morpholino-mediated knock-down technology, we provide evidence that RPTPα is crucial for normal retinal development.

RESULTS AND DISCUSSION

In zebrafish, RPTPα is broadly expressed during development (van der Sar et al., 2001). In the developing eye, RPTPα protein is expressed in the basal border of the eye at 24 hpf, whereas at 3 dpf, it is localized to the inner and outer plexiform layers of the eye as well as to the optic nerve (Fig. 1). To investigate the role of RPTPα in retinal development, we performed functional knock-down experiments in zebrafish by using antisense morpholinos (Nasevicius and Ekker, 2000; Yang et al., 2001; Shepherd et al., 2001; Muller et al., 2001; Bauer et al., 2001).

Antisense morpholinos (-mo) led to knock-down of RPTPα protein as demonstrated by immunoblotting (Fig. 2). RPTPα protein expression was almost completely abolished at 3 dpf in RPTPα-mo-injected embryos, whereas RPTPα protein was readily detected at 4 dpf, demonstrating that RPTPα-mo-induced knock-down was transient. Injection of control morpholinos with inverted sequence did not affect RPTPα expression (data not shown). Taken together, RPTPα-mo injection led to transient knock-down of RPTPα protein expression.

RPTPα-mo-induced RPTPα knock-down caused transient apoptosis in the brain. The knock-down phenotype was characterized by a smaller fore-, mid-, and hindbrain, and an inconspicuous mid/hindbrain boundary (AvdS, DZ, and JdH, unpublished). Interestingly, the eyes of the RPTPα-mo–injected embryos were smaller as well. However, there was no obvious increase in apoptosis in the eye according to TUNEL assays (data not shown). We further investigated the effects of RPTPα-mo–mediated knock-down on eye development by histologic analyses. At 28 hpf, the lens (L) and the pigmented neuroepithelium (Fig. 3A, arrow) were normal in the RPTPα-mo–injected embryos. However, the retina of RPTPα-mo–injected embryos contained fewer cells compared with wild-type retinae (Fig. 3A compare left with right), causing the reduction in eye size.

At 3 dpf, the retinae of wild-type embryos were well organized and all five layers, from retinal ganglion cells to the rods and cones, were clearly differentiated (Fig. 3C, left panel). In contrast, at 3 dpf, the size of the eye

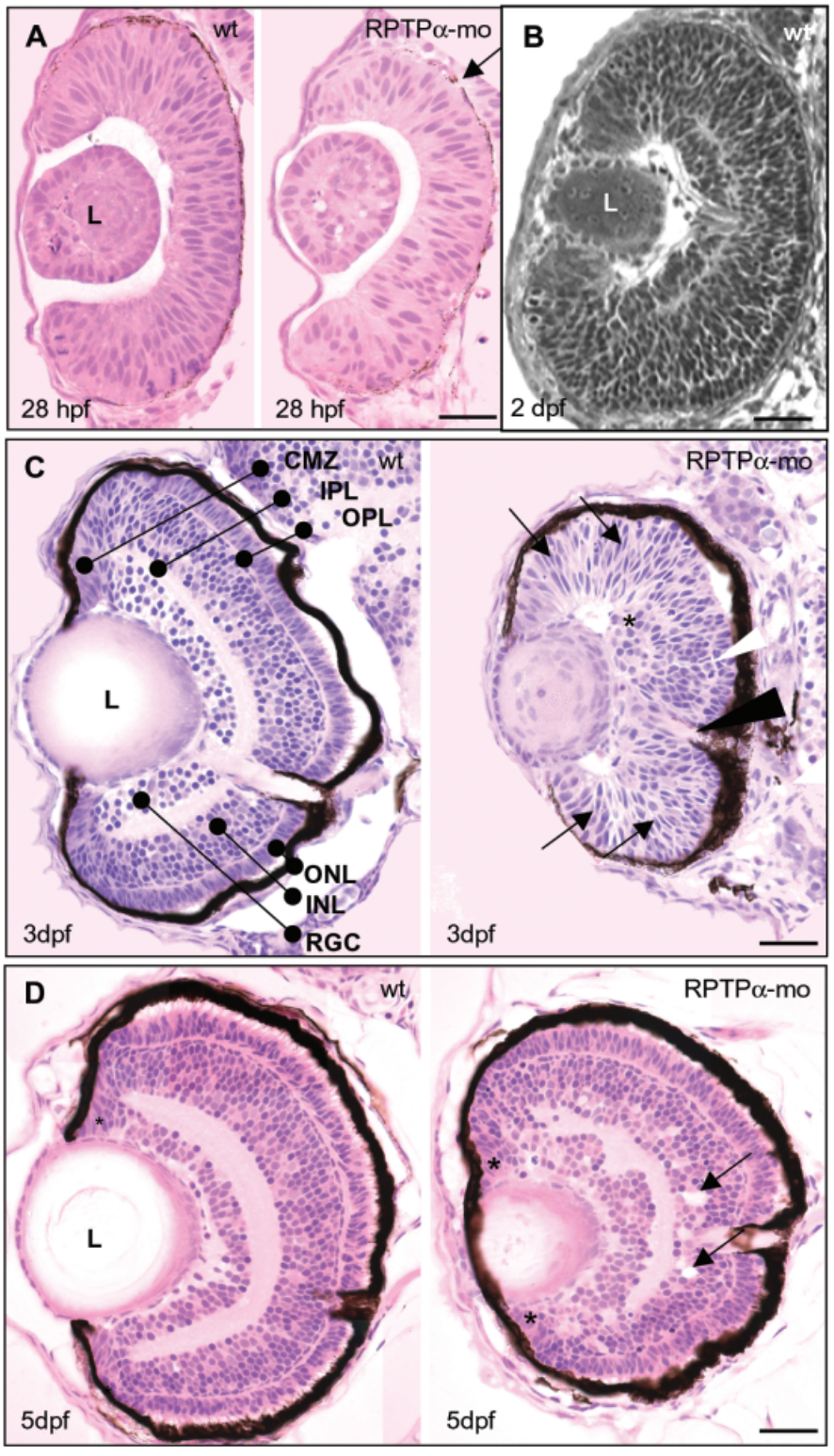

Fig. 3. Receptor protein-tyrosine phosphatase alpha (RPTPα) knock-down–induced defects in eye development. Retinal organization of wild-type (left panels) and RPTPα-morpholino (-mo) -injected embryos (right panels). Transverse median sections through the eye of embryos at different developmental stages. **A:** At 28 hours postfertilization (hpf), the neural retina of RPTPα-mo–injected embryos consists of fewer cells compared with wild-type (wt) retinae. The arrow indicates the pigmented neural epithelium. **B:** Transverse section of a 2-days postfertilization (dpf) -old embryo. The retina already shows lamellar organization (see also: http://imaging.niob.knaw.nl/). **C:** At 3 dpf, the neural retina of RPTPα-mo–injected embryos are largely undifferentiated (arrows) and only in the central region some rudimentary lamellar organization can be observed. Overall, the size of the eye is reduced compared with wild-type embryos. The asterisk indicates potential retinal ganglion cells, the white arrowhead indicates potential outer plexiform layer, and the black arrowhead indicates the optic nerve. **D:** At 5 dpf, the retinae of RPTPα-mo–injected embryos contain five layers and most cells are differentiated. Asterisks indicate the ciliary marginal zones, arrows indicate gaps in the amacrine cell layer of the inner nuclear cell layer. At least three embryos were examined per stage, and representative sections are depicted here. L, lens; CMZ, ciliary marginal zone; RGC, retinal ganglion cells; IPL, inner plexiform layer; INL inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer. Scale bars = 50 μm in A,C,D, 60 μm in B.

of RPTPα-mo–injected embryos was reduced and the retinae lacked obvious layered organization (Fig. 3C, right panel). Based on morphology, it appeared that most cells were phenotypically indistinguishable from retinal cells of 28-hpf embryos (Fig. 3A, left panel) and, therefore, most likely undifferentiated (compare Fig. 3C, right panel, arrows with Fig. 3A, left panel). However, in the central region of the retina the optic nerve

was formed, indicating that some retinal ganglion cells must have differentiated (Fig. 3C, right panel, arrowhead). Additional indications for differentiation were the rounded cells in the region where normally the retinal ganglion cells reside (RGC) (Fig. 3C, right panel, asterisks) as well as a rudimentary OPL (Fig. 3C right panel, white arrowhead). The undifferentiated and unorganized state of the retina of RPTPα-mo–injected embryos at 3 dpf was not merely due to retardation in development, because the retina of a wild-type embryo at 2 dpf already shows laminar organization (Fig. 3B, see also Malicki et al., 1996; Verbeek et al., 2000). Moreover, other developmental landmarks in the embryo such as pigmentation and the presence of fin buds confirmed that general development was not delayed.

Strikingly, at 5 dpf, although the size of the eyes was still reduced compared with wild-type eyes (Fig. 3D), the layered organization of the retina of RPTPα-mo–injected embryos is largely restored (Fig. 3D, right panel compare with wild-type Fig. 3D, left panel). Undifferentiated cells are confined to the ciliary marginal zone (CMZ) where the progenitor cells are located (asterisks, Fig. 3D). Although all layers were present, the RGC layer was loosely organized lacking a continuous boundary and the amacrine cell layer contained large acellular gaps (Fig. 3D, right panel, arrows), suggesting that certain cell types were absent. The observed partial recovery of retinal development at 5 dpf (Fig. 3D) coincided with re-expression of RPTPα protein (Fig. 1), suggesting that some of the cells had retained the potential to differentiate and form a layered retina later during development.

To study eye morphology at 3 dpf in more detail, we sectioned RPTPα-mo–injected embryos and carried out immunohistochemistry with anti-RPTPα antibody (AP5478) (den Hertog et al., 1996). Wild-type 3-dpf embryos expressed RPTPα protein in the optic nerve (Fig. 4A, arrow 1), the inner plexiform layer (IPL, Fig. 4A, arrow 2), and the outer plexiform layer (OPL, Fig. 4A, arrow 3). Double labeling of wild-type embryos with anti-acetylated tubulin, a marker for most axon tracts (Chitnis and Kuwada, 1990), demonstrated staining of the IPL (Fig. 4B, arrow 2), the OPL (Fig. 4B, arrow 3), and the optic nerve (Fig. 4B, arrow 1). As expected, RPTPα protein was absent from the retinae of RPTPα-mo–injected embryos at 3 dpf (Fig. 4C). Anti-acetylated tubulin staining was absent from eyes of RPTPα-mo–injected embryos (Fig. 4D), except for the optic nerve of RPTPα-mo–injected embryos (Fig. 4D, arrow 1). The fasciculation of the optic nerve appeared to be absent, because it consisted of three smaller axon bundles instead of one thick bundle as in wild-type embryos. Therefore, at least some retinal ganglion cells had differentiated and grown axons, although they did not fasciculate properly.

In summary, the retinal phenotype of RPTPα is characterized by delayed and abnormal differentiation. At 3 dpf, retinae of RPTPα-mo–injected embryos lacked

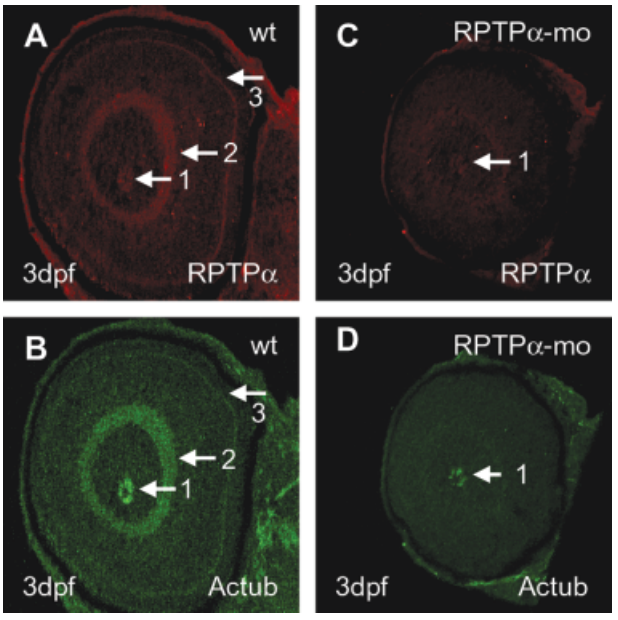

Fig. 4. Defects in retinal organization and differentiation in receptor protein-tyrosine phosphatase alpha morpholino (RPTPα-mo) -injected embryos. **A,B:** Oblique section of 3-days-postfertilization (dpf) -old wild-type (wt) embryo labeled with polyclonal anti-RPTPα antibody (AP5478; A) and anti-acetylated tubulin (B). Labeling is found in the optic nerve (arrow 1), the inner plexiform layer (arrow 2), and the outer plexiform layer (arrow 3). **C,D:** Oblique section of 3-dpf-old RPTPα-mo–injected embryo labeled with polyclonal anti-RPTPα antibody (AP5478; C), and anti-acetylated tubulin (Actub) antibody (D). Labeling of RPTPα and acetylated tubulin is found in the optic nerve (arrow 1), all other structures labeled in wild-type are not labeled in RPTPα-mo–injected embryos.

lamination, cells maintained their elongated undifferentiated morphology and acetylated tubulin, a marker for differentiated axons, was absent. A prerequisite for a precursor cell in the retina to migrate to its appropriate laminar position is to have exited mitosis first. This in conjunction with the absence of axonal labeling may suggest that the absence of lamination in RPTPα-mo–injected embryos is due to persistent cell cycling of retinal cells that lack RPTPα. This phenotype is somewhat reminiscent of the retinal phenotype of *perplexed* mutants in which retinal cells remain elongated and continue to proliferate. Link et al. (2001) postulate that, in *perplexed* embryos, there is a developmental block at the neuroepithelial stage and that molecules essential for the transition from proliferative to postmitotic stage such as PTEN may be implicated. The retinal phenotype of RPTPα-mo–injected embryos and *perplexed* mutants is similar, suggesting that RPTPα may play a role in this transition. If the retina continues to proliferate in RPTPα-mo–injected embryos, like in *perplexed* mutants, then the question arises, Why does the eye remain small? A possible explanation given by Link et al. (2001) for *perplexed* retinae and by inference also for RPTPα-mo–injected embryos is that the cell cycle may be slow in *perplexed* retinae. A possibility then is that normal kinetics of apoptosis affects

cell numbers to a greater extent, thus resulting in less cells and, thus, smaller eyes.

Because the RPTPα-mo–mediated knock-down is transient, our results are particularly difficult to interpret, as we do not know what aspects of the partial rescue of the phenotype are attributable to de novo translated RPTPα later in development. That the RPTPα-mo–injected embryos at 5 dpf displayed an abnormal development of the amacrine cell layer that is characterized by acellular pockets (Fig. 3) suggests that a specific cell population has been lost by the RPTPα knock-down. Interestingly, acellularity of the amacrine cell layer is also a characteristic of the retinae of the *perplexed* mutant, suggesting that slow cell cycle in combination with steady state normal apoptosis may underlay the phenotype. Concerning amacrine cell differentiation, it is interesting to note that overexpression of the *Xenopus* proneural gene Xath5 in tadpoles biases retinal progenitors toward a retinal ganglion cell fate at the expense of other retinal cell types such as bipolar cells, amacrine cells, and Muller glia (Kanekar et al., 1997). Moreover, loss of function of zf Ath5 in *lakritz* mutant embryos results in ectopic amacrine cells (Kay et al., 2001). Our data do not allow definitive conclusions about possible cell transfating in retinae of RPTPα-mo–injected embryos. Specific acellular regions in the amacrine layer of the RPTPα-mo–injected embryos may suggest that in the RPTPα-mo–injected embryos, the first wave of neurogenesis uses up most of the progenitors, leaving insufficient precursors for the second wave during which amacrine cells are generated. Alternatively, the switch to the second wave of neurogenesis may be delayed because of the slower cell cycle of the second wave precursors so that the first wave continues to generate retinal ganglion cells. Finally, the first wave of neurogenesis may build both layers simultaneously. Because the most notable phenotype of the RPTPα-mo–injected embryos concerns delayed retinal differentiation, the transfating as discussed above does not seem likely to be the primary cause of the phenotype. Experiments aimed at identification of specific neuronal subpopulations that are affected in the retinae of RPTPα-mo–injected embryos will provide answers to the above questions.

EXPERIMENTAL PROCEDURES

Animals

Zebrafish embryos were collected form a laboratory breeding colony kept at 27.5°C on a 14:10 hr light/dark rhythm, as previously described (van der Sar et al., 1999). Embryos were staged at 28.5 °C according to hours postfertilization, days post fertilization, and morphologic criteria (Kimmel et al., 1995).

Morpholino injection and histology

Morpholinos were obtained from Gene Tools. RPTPα-mo was complementary to the start codon of zf-RPTPα (accession no. Y15874); sequence: 5′-TGCCCTGGAGAAACGTAACCTGCAT-3′. A morpholino with inverted sequence was used as control. Routinely, 0.5 ng of morpholino was injected per embryo at the 1-cell stage. This amount of morpholino greatly reduced RPTPα expression without nonspecific side effects.

Embryos were collected at appropriate time points, fixed in 4% paraformaldehyde (W/V) (O/N 4°C), rinsed in phospate buffered saline (PBS), and processed for sectioning. Plastic transverse 7-μm-thick sections were made of 28 hpf, 3 dpf, and 5 dpf wild-type or RPTPα-mo–injected embryos. In addition, sagittal 7-μm-thick sections were made of 2-dpf-old wild-type embryos. All sections were counterstained with hematoxylin and eosin.

Immunoblotting and immunohistochemistry

Embryos were pooled and lysed in cell lysis buffer (50 mM HEPES pH 7.4, 150 mM NaCl, 1 mM $MgCl_2$, 10% glycerol, 1% Triton X-100, and protease inhibitors). Thirteen to 15 embryo equivalents were loaded onto a 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis gel. The gel was blotted onto a polyvinylidene difluoride membrane and probed with affinity purified anti-RPTPα antibodies (AP5478; den Hertog et al., 1996), washed extensively, incubated with horseradish peroxidase coupled secondary goat anti-rabbit antibody, washed extensively, and developed by using enhanced chemiluminescence.

Embryos were collected at appropriate time points, fixed in 4% paraformaldehyde (W/V) (O/N, 4 °C), rinsed with PBS, and processed for sectioning. Paraffin sagittal sections of 7 μm were made of 3-dpf wild-type and RPTPα-mo–injected embryos. Sections were deparaffinized and washed several times in PBS before blocking for 1 hr (PBS, 0.1% Tween-20, 1% bovine serum albumin, 2% normal lamb serum). Affinity purified anti-RPTPα antibody (AP5478) (den Hertog et al., 1996) was added, and embryos were incubated overnight at 4°C. After washing with PBS containing 0.1% Tween-20 (PBS-T), sections were incubated for 2 hr at room temperature in secondary antibody, swine anti-rabbit CY3-conjugated antibody. After several wash steps (PBS-T), sections were subsequently labeled overnight at 4°C by using a monoclonal anti-acetylated tubulin antibody (Sigma). After washing (PBS-T), sections were incubated for 2 h aat room temperature in secondary antibody, goat anti-mouse CY5-conjugated antibody. After washing (PBS-T), sections were embedded in Aquamount and viewed by using a Confocal Laser Scanning Microscope (Leica).

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