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Neuronal expression of fibroblast growth factor receptors in zebrafish

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ABSTRACT

Fibroblast growth factor (FGF) signaling is important for a host of developmental processes such as proliferation, differentiation, tissue patterning, and morphogenesis. In vertebrates, FGFs signal through a family of four fibroblast growth factor receptors (FGFR 1-4), one of which is duplicated in zebrafish (FGFR1). Here we report the mRNA expression of the five known zebrafish fibroblast growth factor receptors at five developmental time points (24, 36, 48, 60, and 72 h postfertilization), focusing on expression within the central nervous system. We show that the receptors have distinct and dynamic expression in the developing zebrafish brain, eye, inner ear, lateral line, and pharynx. In many cases, the expression patterns are similar to those of homologous FGFRs in mouse, chicken, amphibians, and other teleosts.

Fibroblast growth factors (FGFs) are found in all metazoans and control many aspects of embryonic development. In particular, FGF signaling is required for proper proliferation, differentiation, and coordinated cell movement (Dorey and Amaya, 2010), and has known roles in processes such as mesoderm formation, axis specification, and limb development (Thisse and Thisse, 2005). Furthermore, FGFs function in many stages of neural development, including tissue patterning, neuronal migration, axon guidance, and synaptogenesis (Guillemot and Zimmer, 2011).

There are 22 identified FGFs in vertebrates (Itoh and Ornitz, 2011; Pownall and Isaacs, 2010). These diffusible ligands signal through a family of four tyrosine kinase receptors, the FGF receptors (FGFR1-4). Upon formation of an FGF-hepar an sulfate-FGFR complex, FGFRs dimerize and initiate a variety of intracellular signal transduction events (Bottcher and Niehrs, 2005; Dorey and Amaya, 2010; Pownall and Isaacs, 2010). Multiple factors determine which FGFs and FGFRs can interact *in vivo*. The four FGF receptors have distinct expression patterns, which change over time (Ota et al., 2010). Furthermore, each FGFR contains three extracellular immunoglobulin-like domains, which control FGF binding specificity and affinity. *In vitro* studies have characterized the activity of different FGF-FGFR combinations, demonstrating significant selectivity (Zhang et al., 2006). Complexity is added by multiple splice forms of each FGFR (Zhang et al., 2006), and in zebrafish, the existence of a second copy of FGFR1 resulting from genome duplication (Rohner et al., 2009).

Given that FGF signaling is important for a host of developmental events, expression patterns can aid us in identifying novel roles for these molecules. Zebrafish is an amenable and versatile model organism for the study of FGF signaling during development. Although expression of the five FGFRs has been well characterized through the period of somitogenesis up until 24 h post fertilization (hpf; Ota et al., 2010), expression data for later embryogenesis, when neurons are migrating and sending out axons, is only available for select genes, developmental times, and in some cases, select organs (Nakayama et al., 2008; Nechiporuk et al., 2005; Regan et al., 2009; Rohner et al., 2009; Scholpp et al., 2004; Sleptsova-Friedrich et al., 2001; Tamimi et al., 2006; Thisse and Thisse, 2005; Thisse et al., 2008; Tonou-Fujimori et al., 2002). This paper provides expression data for the five known zebrafish FGFRs at five developmental time points between 24 and 72 h postfertilization hpf, focusing mainly on neuronal expression.

1. Results

1.1. *fgfr1a* expression

At 24 hpf (Fig. 1A–D), *fgfr1a* is expressed weakly throughout the central nervous system, with stronger expression in the midbrain–hindbrain boundary (Fig. 1B), lens (Fig. 1C), ventral midbrain (Fig. 1D), and tailbud (not shown). At 36 hpf (Fig. 1E–H), *fgfr1a* continues to be expressed in the lens (Fig. 1G), tailbud (not shown), midbrain (Fig. 1H) and midbrain–hindbrain boundary (Fig. 1E and F), with additional expression in the thalamus (Fig. 1G). Tissue surrounding the midbrain tectal ventricle expresses *fgfr1a* at 48 hpf (Fig. 1L). From 48 to 72 hpf, expression is observed in the

Abbreviations: Hpf, hours postfertilization; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor.

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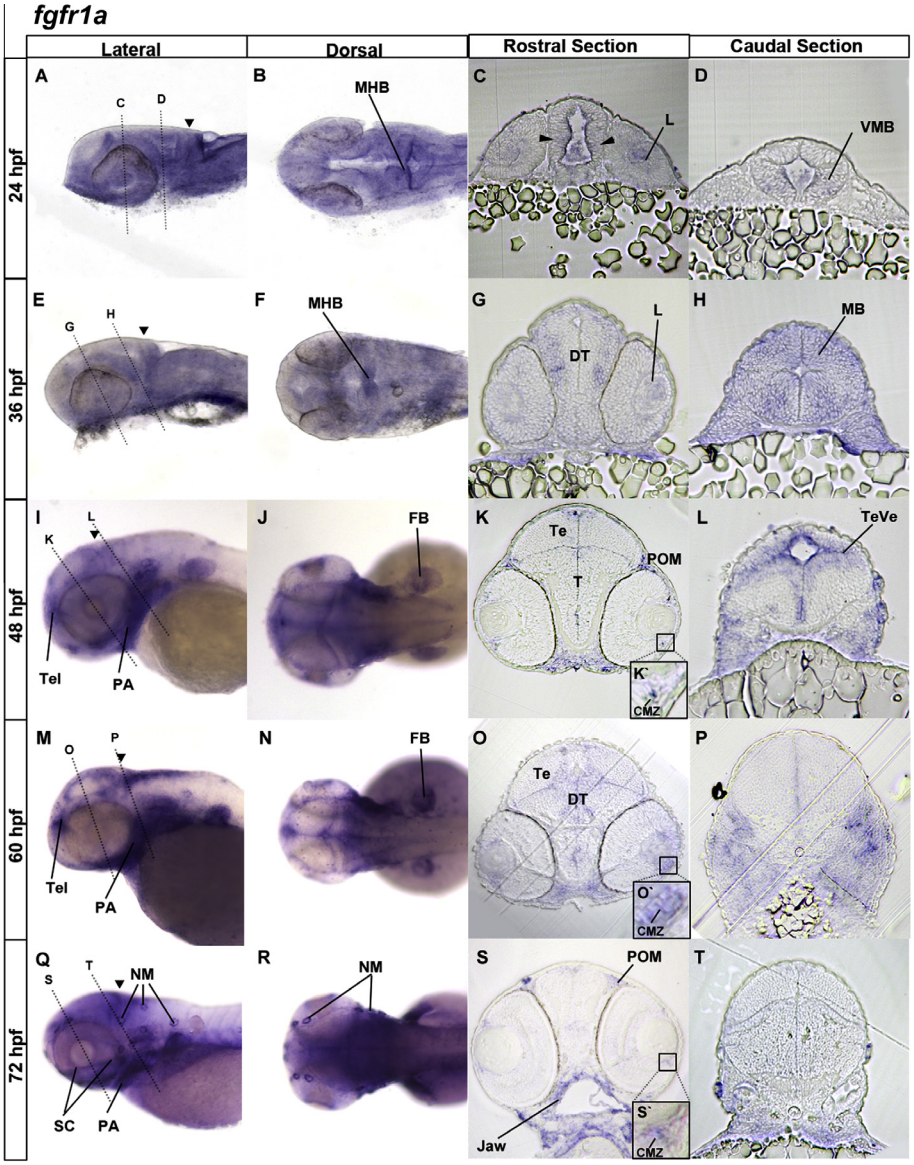

Fig. 1. *In situ* hybridization of *fgfr1a* gene expression. *In situ* hybridization of *fgfr1a* gene expression at 24 hpf (A–D), 36 hpf (E–H), 48 hpf (I–L), 60 hpf (M–P), and 72 hpf (Q–T). Lateral views (A, E, I, M, Q) with anterior to the left, dorsal at the top, dorsal views (B, F, J, N, R) with anterior to the left, rostral transverse brain sections (C, G, K, O, S), and caudal transverse brain sections (D, H, L, P, T). Dotted lines indicate approximate orientation of imaged sections. Solid arrowheads indicate the location of the midbrain–hindbrain boundary. Arrowheads in C point to weak brain expression. Labels point to expression in the ciliary marginal zone (CMZ), dorsal thalamus (DT), fin bud (FB), jaw (J), lens (L), midbrain (MB), midbrain–hindbrain boundary (MHB), midbrain tegmentum (T), neuromasts (NM), optic tectum (Te), pharyngeal arches (PA), periocular mesenchyme (POM), splanchnocranium (SC), tectal ventricle (TeVe), telencephalon (Tel), and ventral midbrain (VMB).

pharyngeal arches (Fig. 1I, M, Q), fin bud (Fig. 1J and N), neuromasts (Fig. 1Q and R) and lateral line (data not shown), periocular mesenchyme (Fig. 1K, O, S), and the proliferative ciliary marginal zone of the peripheral retina (Fig. 1K′, O′, S′). At 72 hpf, *fgfr1a* mRNA is also present in the jaw (Fig. 1S).

1.2. *fgfr1b* expression

At 24 hpf (Fig. 2A–D) and 36 hpf (Fig. 2E–H), *fgfr1b* expression in the central nervous system is diffuse, with higher intensity staining in the ventral diencephalon and ventral retina (Fig. 2C and G). From 48 to 72 hpf (Fig. 2I–T), *fgfr1b* is expressed in the ventricular zones of the brain (Fig. 2J, K, L, N, O, R, S), pharyngeal arches (Fig. 2I, M, Q), fin bud (Fig. 2J, N, R), periocular mesenchyme (Fig. 2K, O, S), and the optic nerve head, where retinal ganglion cell axons exit the eye (Fig. 2K, O, S). During this time *fgfr1b* is also expressed near the midbrain–hindbrain boundary, and in lens and tissue, potentially periocular mesenchyme or blood vessels, surrounding the lens (Fig. 2K, O, S). In addition, *fgfr1b* is expressed in the ciliary marginal zone at 48 and 60 hpf (Fig. 2K and O) and in neuromasts at 72 hpf (Fig. 2R).

1.3. *fgfr2* expression

At 24 hpf, *fgfr2* is expressed in the diencephalon (Fig. 3A and B), midbrain (Fig. 3A), hindbrain (Fig. 3D), otic placodes (Fig. 3B), lens (Fig. 3C), and ventricles (Fig. 3B and C). At 36 hpf (Fig. 3E–H), expression is present in the midbrain (Fig. 3E, H), diencephalon (Fig. 3E and G), and hindbrain (Fig. 3E and F), while expression in the otic placodes (Fig. 3F), and lens (Fig. 3G) is sustained. There