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Signalling pathways in trophic skeletal development and morphogenesis: Insights from studies on teleost fish

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ABSTRACT

During the development of the vertebrate feeding apparatus, a variety of complicated cellular and molecular processes participate in the formation and integration of individual skeletal elements. The molecular mechanisms regulating the formation of skeletal primordia and their development into specific morphological structures are tightly controlled by a set of interconnected signalling pathways. Some of these pathways, such as Bmp, Hedgehog, Notch and Wnt, are long known for their pivotal roles in craniofacial skeletogenesis. Studies addressing the functional details of their components and downstream targets, the mechanisms of their interactions with other signals as well as their potential roles in adaptive morphological divergence, are currently attracting considerable attention. An increasing number of signalling pathways that had previously been described in different biological contexts have been shown to be important in the regulation of jaw skeletal development and morphogenesis. In this review, I provide an overview of signalling pathways involved in trophic skeletogenesis emphasizing studies of the most species-rich group of vertebrates, the teleost fish, which through their evolutionary history have undergone repeated episodes of spectacular trophic diversification.

Contents

Abbreviations: Ahr, Aryl hydrocarbon receptor pathway; BMPs, bone morphogenetic proteins; Ca^{2+}/CaM, Calcium/calmodulin signalling; Dll, delta-like transmembrane ligand; Dlx, Distal-less homeodomain transcription factor; ECM, Extracellular matrix; Edns, Endothelins; EGFR, epidermal growth factor receptor; ER, oestrogens/estrogen receptor; ERK, extracellular signal-regulated kinase; FGFs, fibroblast growth factors; GC, glucocorticoid; GR, glucocorticoid receptor; Hox, homeobox transcription factor; Hh, Hedgehog signalling pathway; IGFs, Insulin-like growth factors; IGFBPs, Insulin-like growth factor binding proteins; JNK, c-Jun NH2-terminal kinase; MAPKs, mitogen-activated protein kinases; MMP, matrix metalloproteinase; NO, Nitric oxide pathway; NFAT, nuclear factor of activated T-cells; OPG, Osteoprotegerin; OSX, Osterix; PI3K, phosphatidylinositide 3-kinases; PTH, Parathyroid hormone; PTHrP, parathyroid hormone-related peptide; RA, Retinoic acid; RANKL, receptor activator of nuclear factor Kappa B ligand or osteoprotegerin ligand; Runx, Runt-related transcription factor; Sox9, sex determining region Y box 9; TGF-βs, transforming growth factor beta superfamily; TF, Transcription factor; WGD, whole genome duplication; Wnt, Wingless-related integration site ligand; 5-HT, 5-hydroxytryptamine or serotonin

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1. Introduction

The formation of the craniofacial skeleton, including trophic structures, requires a highly complicated sequence of developmental events mediated by molecular cross-talk between neural crest cells and other cells originating from all three germ layers (Szabo-Rogers et al., 2010). In spite of the great diversity of trophic skeletal morphologies seen in vertebrates, the principal molecular signals shaping distinct bone and cartilage elements in this region during embryonic development are conserved among distantly related species. Teleost fishes are in many ways valuable model organisms for studies of craniofacial development and diversification. Apart from reflecting some of the primitive states of basic craniofacial elements in vertebrate evolution, the teleost fishes exhibit spectacular cases of adaptive radiation and trophic polymorphism where diversification of trophic structures plays a key role (Hulsey et al., 2005; Braasch et al., 2014; Kratochwil and Meyer, 2015; Powder and Albertson 2016). In Fig. 1, phylogenetic time-trees show the evolutionary status of teleost fish across vertebrates and divergence of some of the major orders within Teleostei, reconstructed based on Broughton et al. (2013).

Teleosts possess seven pharyngeal arches, which are primordia for trophic structures, and contrary to most vertebrates, they often have two sets of toothed jaws (Hulsey et al., 2005). Upon induction of cranial neural crest cells (CNCCs) alongside the developing anterior neural tube, they migrate in streams to specific cranial regions including the pharyngeal arches. CNCCs contribute to the formation of membranous bones in the skull, frontonasal and pharyngeal skeleton. These migratory streams of CNCCs correspond to their origin in different segments adjacent to the diencephalon, mesencephalon and rhombencephalon or rhombomeres 1–7 (r1-r7) (Fig. 2A). The compartmentalization of these regions is the result of specific combinatorial and delimited expression of homeobox transcription factors (TFs) critical for embryonic patterning, most notably, the *Hox* and *Dlx* families of genes. The absence of expression of *Hox* genes in the CNCCs migrating into the first pharyngeal arch is an interesting example of this specificity which is believed to be an evolutionary innovation partly responsible for the acquisition of the oral jaw in gnathostomes (jawed vertebrates) (Kuratani, 2004). The first pharyngeal arch supplies skeletal elements required for the formation of both the upper and lower jaws (Fig. 2B). The second arch provides elements of the hyoid skeleton, and the more posterior arches (3-7) contribute to the formation of the branchial skeleton which provides the building blocks for development of the pharyngeal jaws in teleost fish (Hulsey et al., 2005; Mork and Crump, 2015).

The trophic skeleton in teleosts can be divided into major functional structures, such as the neurocranium, the hyoid and opercular elements and the oral and pharyngeal jaws, based on their cellular origins and distinct gene regulatory codes during early development (Fig. 2C) (Hulsey et al., 2005). The pharyngeal jaws, located at the posterior end of the pharyngeal skeleton, have evolved independently of the oral jaws and are not present in all teleost fish (Hulsey et al., 2005; Wainwright, 2006). Among the gene regulatory codes specifying each of the functional trophic structures, the activity of several sets of genes has been found to be critical during the early developmental patterning in fish (Hulsey et al., 2005). Many of these genes participate in skeletal development and morphogenesis through modular and/or integrated molecular functions along the anterior to posterior and dorsal to ventral body axes. The developmental events during the formation of jaws and other trophic structures have been thoroughly reviewed (Kuratani, 2004; Hulsey et al., 2005; Mork and Crump 2015). Considering the vast number of studies focusing on the molecular underpinnings of these developmental trajectories, it seems timely to review the interconnected signalling pathways that orchestrate the development of trophic skeletal structures. In this review, I focus on several conserved pathways that control or affect jaw development. The pathways are discussed in the context of their specific roles in skeletal development with insights from trophic structures in teleost fish, their relevant molecular targets and cross-talk with other relevant pathways. It should be noted that a substantial part of the current knowledge about these pathways has been acquired from studies of vertebrate species other than teleost fishes (e.g. mouse and chicken). Therefore, in many cases the conservation of the detailed molecular cascades and interactions remains to be formally validated in teleosts.

As a conclusion, I present an overview of the involvement of each of these pathways in early craniofacial patterning and subsequent trophic skeletal morphogenesis and their potential association with trophic diversification in teleost fishes. I then present an example of how pathways interconnect through developmental cascades and a scheme of how some of these pathways show modularity and spatial overlap in shaping skeletal elements of the mouth and pharynx in teleost fish.

2. Signals mediated by BMPs/TGF-βs, Hh, Notch and Wnt proteins: the central pathways orchestrating trophic skeletal development and morphogenesis

2.1. BMPs/TGF-βs superfamily

The transforming growth factor beta (TGF-β) superfamily is comprised of a large number of structurally related polypeptides conserved across the animal kingdom, and most of the TGF-β