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Review

Holmgren's principle of delamination during fin skeletogenesis

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ABSTRACT

During fin morphogenesis, several mesenchyme condensations occur to give rise to the dermal skeleton. Although each of them seems to create distinctive and unique structures, they all follow the premises of the same morphogenetic principle. Holmgren's principle of delamination was first proposed to describe the morphogenesis of skeletal elements of the cranium, but Jarvik extended it to the development of the fin exoskeleton. Since then, some cellular or molecular explanations, such as the "flypaper" model (Thorogood et al.), or the evolutionary description by Moss, have tried to clarify this topic. In this article, we review new data from zebrafish studies to meet these criteria described by Holmgren and other authors. The variety of cell lineages involved in these skeletogenic condensations sheds light on an open discussion of the contributions of mesoderm- versus neural crest-derived cell lineages to the development of the head and trunk skeleton. Moreover, we discuss emerging molecular studies that are disclosing conserved regulatory mechanisms for dermal skeletogenesis and similarities during fin development and regeneration, which may have important implications in the potential use of the zebrafish fin as a model for regenerative medicine.

Contents

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1. Introduction

In a seminal paper (1940), Holmgren stated: "the differentiation of the neural crest mesenchyme takes place successively by delamination of cell laminas". Studying the development of the skull in sharks and rays, this researcher observed that four different cell laminas of various types of bone and cartilage successively appeared to generate the cranial skeleton and part of the meninges. Once formed, each cell lamina "sank in" toward the brain letting a new wave of delamination take place. The first delamination wave formed the rudiments of the orbital cartilage, the medial part of the tenia marginalis, the anterior part of the trabeculae, the trabecular commissure, the rostral plate and the dorsal and lateral parts of the auditory capsule. The supra-orbital cartilage and the lamina orbitonasalis were formed by the second delamination wave, while the antorbital cartilage and the rostral appendix were generated by the third delamination wave. Finally, the placoid scales and the envelopes of the sensory canals were formed by the fourth delamination wave. These delaminations, which are necessary for the formation of all skeletal components of the cranium, occur by mesenchyme condensation beneath the ectoderm. Each one involves a very restricted region of the embryo where other condensations may also occur at later stages. This classic description by Holmgren thus provides a special perspective to study the development of the craniofacial skeleton (Holmgren, 1940). Since this early study, mesenchyme condensations have been found in many other organs and developmental stages of the embryo.

After Holmgren's paper, Erik Jarvik proposed in 1959 that the above-mentioned interpretation should be named "Holmgren's principle of delamination" and that this could also be applied to the generation of the actinopterygian fins. After a profound paleontological study, Jarvik suggested that different delamination events could be the basis of the formation of the exoskeletal component of fins from elasmobrachii to teleostei. This exoskeleton involves the ceratotrichia, the actinotrichia, the lepidotrichia, the camptotrichia, the scales, the scutes, the spines and the dental plates. In Jarvik's discussion, other potential neural crest-derived tissues, such as the dermal bones of fish, the heads of armadillos, the antlers of deer or the shells of turtles, were also dependent on this process (Jarvik, 1959). In the early actinopterygian fishes, the dermal skeleton usually showed the odontogenic tissues, dentine and enamel, deposited over the bone. Whereas these odontogenic tissues have been proposed to evolve from a common ancestral tissue, the odontode (Reif, 1982; Sire and Huysseune, 2003; Sire et al., 2009), there is not such a hypothesis for the osteogenic component. Following this view, the search for a common mechanism underlying mesenchyme condensation in head and fins should disclose features of an ancestral osteogenic delamination.

The molecular paradigm is using the zebrafish, *Danio rerio*, as a model species for studies of fish development in Teleostomi. In recent years, developmental genetics has provided a better understanding of the morphogenesis of many organs. Old questions, such as fin skeletogenesis, are now amenable to re-evaluation (Akimenko et al., 2003). As an example, fin delaminations in zebrafish, now described in cellular and molecular terms, could be re-evaluated under the classical Holmgren's proposal. In this review, we will briefly describe advances in craniofacial condensation studies and then those on fin exoskeletal delaminations, subjects poorly studied until now. Unfortunately, the zebrafish fin exoskeleton only shows actinotrichia, lepidotrichia and scales. In order to study the other elements of the fin exoskeleton in the future, this comparative approach should be applied to appropriate fish species.

On the one hand, the cranial bones in zebrafish have been the subject of a number of developmental and regenerative studies (Fig. 1A–D; e.g. Cubbage and Mabee, 1996; Geurtzen et al., 2014; Kague et al., 2012; Tran et al., 2010; Verreijdt et al., 2006). These authors describe that bones are derived from either neural crest or mesoderm cells (Fig. 1E, F; Kague et al., 2012). However, important variations in origin are observed when bones in the zebrafish are compared with those in other vertebrate species (see Hall, 2005). Nevertheless, these cell lineages have not been studied in much detail and only a small number of gene functions have been published. For instance, in mammals, a specific ectomesenchymal stem cell lineage has been shown to give rise to a final osteoblast that synthesizes the cranial bone (Bhatt et al., 2013; Bronner and LeDouarin, 2012; Simões-Costa and Bronner, 2013), but this is not known in zebrafish in such detail.

On the other hand, many molecular and developmental studies have focused on the formation of rays and scales during embryogenesis (rev. Marí-Beffa and Murciano, 2010; Sire and Akimenko, 2004) or regeneration (rev. Akimenko et al., 2003; Iovine, 2007; Marí-Beffa and Murciano, 2010). The rays are the dermoskeletal elements of the fins of actinopterygians and show actinotrichia and lepidotrichia, two fish-specific skeletal tissues. Scales are also present beneath the epidermis, in proximal positions of the fins (Fig. 2A) and over the whole body. Different cell lineages have also been described to occur during fin development and regeneration (Knopf et al., 2011; Sousa et al., 2011; Stewart and Stankunas, 2012; Tu and Johnson, 2011), but their embryological origin from either neural crest or mesoderm is under intense debate (Kague et al., 2012; Lee et al., 2013a, 2013b; Shimada et al., 2013; Smith et al., 1994).