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Review

The pharyngeal pouches and clefts: Development, evolution, structure and derivatives

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ABSTRACT

The pharyngeal arches form the face and neck of the developing embryo. The pharyngeal tissue is divided into distinct arches by the formation of clefts and pouches in between the arches. These clefts and pouches form at the juxtaposition between the ectoderm and endoderm and develop into a variety of essential structures, such as the ear drum, and glands such as the thymus and parathyroids. How these pouches and clefts between the arches form and what structures they develop into is the subject of this review. Differences in pouch derivatives are described in different animals and the evolution of these structures are investigated. The implications of defects in pouch and cleft development on human health are also discussed.

Contents

1. The emergence and development of the pharyngeal arches

In vertebrates, the pharyngeal apparatus develops from a transient series of segmental structures appearing as bulges on the cranial lateral side of the embryo and named the pharyngeal, or branchial, arches. The pharyngeal arches form successively in a cranial to caudal way during ontogeny. Five pairs of arches emerge between the second and fourth week of gestation in man, between Theiler's stages St13 and -16 in the mouse, and between Hamburger and Hamilton stages HH14 and -19 in the chick [1–3]. Notably, in all amniotes, the fifth arch does not form or regresses. Consequently, the most caudal arch corresponds to the sixth arch, which remains rudimentary. In non-amniotes, the fifth arch is maintained and an additional posterior arch develops [4]. Thus, in the zebrafish, from the second to the third day after fertilization, a total of seven arches emerge [5]. Eight and nine arches are also observed in some chondrichthyans, while the lamprey, a jawless agnathan, has nine arches [6].

During evolution there appears to be a general trend towards loss of pharyngeal arches and pouches. In keeping with this, many fossil fish have high numbers of arches, with ostracoderm fossils discovered with as many as 30 arches [7]. This general trend in reduction in the number of posterior arches may reflect the changing function of the caudal pharyngeal regions, as the requirement for multiple gill supports was lost during the move from water to land.

In the jawed vertebrates the first arch divides into two clearly identifiable subunits termed the maxillary and the mandibular arches, which expand ventrally to form the upper and lower jaw. In agnathans (jawless vertebrates), the mouth forms between the first arch (mandibular) crest and the more anterior pre-mandibular

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crest [8]. The upper and lower lips of a lamprey are therefore not homologous to the upper and lower jaw of a jawed vertebrate. This change in position of the mouth appears to have occurred through changes in the area over which signalling molecules, such as *Fgfs* (Fibroblast growth factors) and *Bmps* (Bone morphogenetic proteins), act to define the initial mouth region, and as such is a good example of how a relatively small early heterotopic shifts can lead to major changes in resulting structures [8].

The pharyngeal arches are composed of tissues derived from the three embryonic germ layers. Indeed, each arch is covered on the outside by ectoderm, and on the inside by endoderm. Its core is of mesoderm origin and is surrounded by neural crest-derived mesenchyme. As development proceeds, in between the arches, the lateral wall of the pharynx evaginates forming an out-pocketing known as the pharyngeal pouch, whereas, externally, the overlying ectoderm depresses forming a groove termed the pharyngeal cleft. As a result of these movements, the endoderm and ectoderm physically contact forming a closing membrane [3,4,9]. Cells within the pouch endoderm have high levels of actin fibres that form a web of supra-cellular actin cables. These cables appear to direct expansion of the pouch thereby controlling pouch morphogenesis, and, in keeping with this, disruption of the cables leads to abnormal pouch formation [10].

Over the course of embryogenesis, all the arch components differentiate into distinct derivatives. Specifically, the neural crest develops into the skeleton, the connective tissues, and part of the neurosensory ganglia of the cranium [11,12]; the mesoderm forms the head and neck muscles, skeletal elements, such as the cranial base, and blood vessels [13,14]; the arch ectoderm gives rise to the oral epithelium, the keratinized epidermis of the face and the throat, as well as the sensory neurons of the epibranchial ganglia [11,15] and the arch endoderm forms the pharynx epithelium and glands [3,9,16]. The pharyngeal pouches and clefts are also regionalized to generate specific tissues and organs (Fig. 1).

The segmentation of the pharyngeal region appears to be driven by the endoderm [6]. Pharyngeal segmentation is a general feature of chordates and is found in animals without apparent neural crest, as observed in the cephalochordate amphioxus. The segmented pharynx of cephalochordates, hemichordates and urochordates is homologous to that of vertebrates, as shown by their shared expression of genes such as the paired motif transcription factors *Pax1/9* [17]. From developmental studies, ablation of the neural crest does not affect the initial formation and patterning of the endodermal pouches [18], again suggesting that the first stages of pouch development are independent of the crest that migrates into them. In zebrafish mutants where the endoderm is defective the pouches fail to form and as a consequence the pharyngeal region is severely disrupted [19]. At these early stages, the endoderm plays a role in patterning the surrounding arches. In the chick, excision of the foregut endoderm leads to a failure in development of specific parts of the pharyngeal skeleton, while ectopic grafts of foregut endoderm leads to duplication of skeletal elements [20]. In the zebrafish the endoderm has been shown to be essential for the identity, survival and differentiation of chondrogenic neural crest [21]. Many key signalling molecules are found expressed in the endoderm of the forming pharyngeal pouches, including *Shh* (*Sonic hedgehog*), *Fgfs*, and *Bmps* [18]. Shh from the foregut endoderm has been shown to play a key role in inducing expression of *Fgf8* in

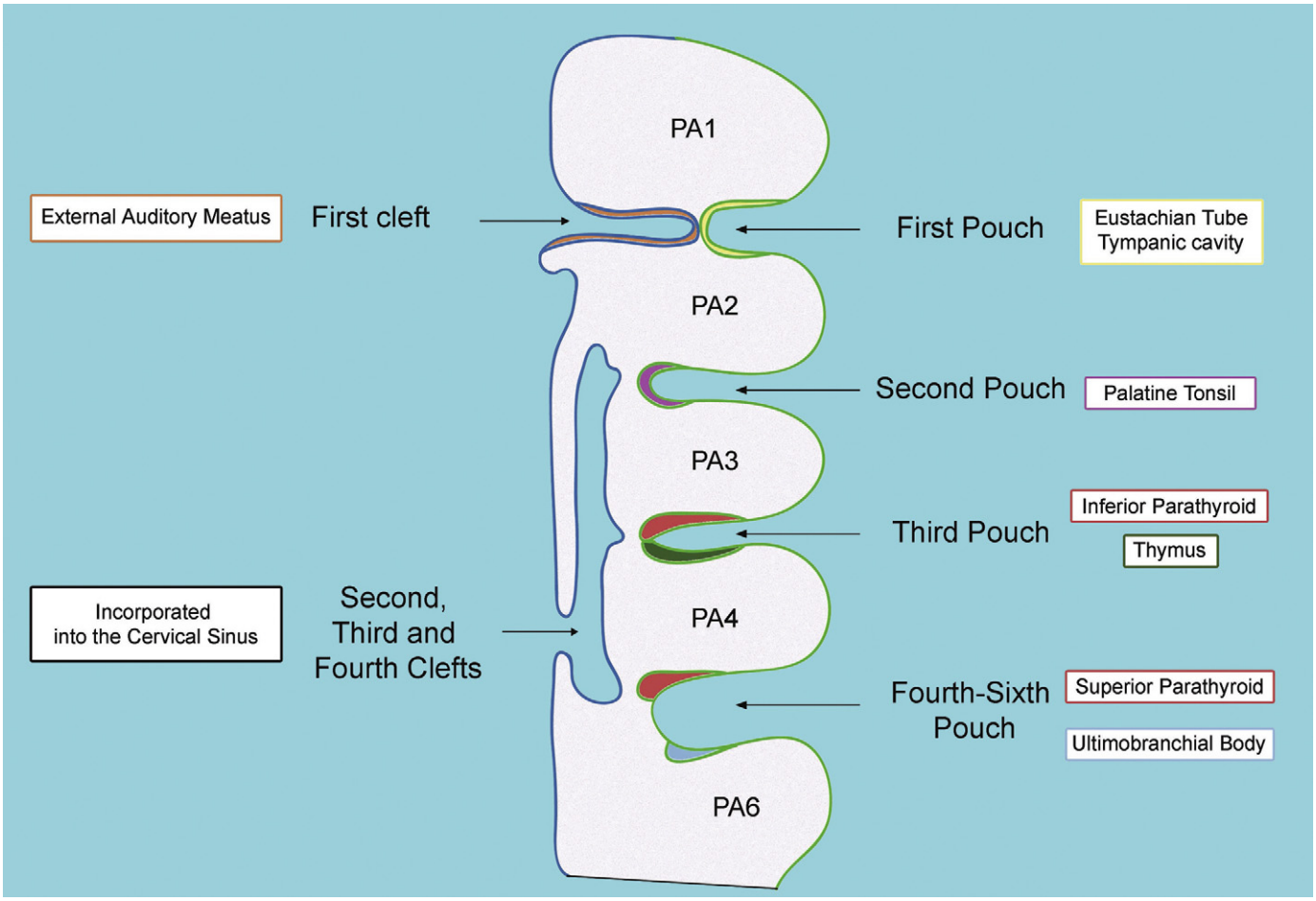

Fig. 1. Derivatives of the pharyngeal clefts and pouches in humans. PA = pharyngeal arch.