Establishing the pre-placodal region and breaking it into placodes with distinct identities

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ABSTRACT

Specialized sensory organs in the vertebrate head originate from thickenings in the embryonic ectoderm called cranial sensory placodes. These placodes, as well as the neural crest, arise from a zone of ectoderm that borders the neural plate. This zone separates into a precursor field for the neural crest that lies adjacent to the neural plate, and a precursor field for the placodes, called the pre-placodal region (PPR), that lies lateral to the neural crest. The neural crest domain and the PPR are established in response to signaling events mediated by BMPs, FGFs and Wnts, which differentially activate transcription factors in these territories. In the PPR, members of the Six and Eya families, act in part to repress neural crest specific transcription factors, thus solidifying a placode developmental program. Subsequently, in response to environmental cues the PPR is further subdivided into placodal territories with distinct characteristics, each expressing a specific repertoire of transcription factors that provide the necessary information for their progression to mature sensory organs. In this review we summarize recent advances in the characterization of the signaling molecules and transcriptional effectors that regulate PPR specification and its subdivision into placodal domains with distinct identities.

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Introduction

During the evolution of the vertebrate head, a number of specialized sensory organs arose that are derived from thickenings in the embryonic ectoderm called cranial sensory placodes. During gastrulation, the embryonic ectoderm is separated into neural and non-neural domains by signals from underlying tissues such as the organizer in frogs and the hypoblast in amniotes. Subsequent interactions lead to the expression of different sets of transcription factors in the neural and non-neural ectoderms whose expression overlaps in an intermediate ectodermal domain, herein referred to as the neural border (NB) zone. This region will give rise to a large number of cell types that include the precursors of the peripheral nervous system. The derivatives of this intermediate domain include the neural crest and the cranial sensory placodes. The precursor region of the placodes is first recognizable as a U-shaped domain restricted to the anterior border of the neural plate called the pre-placodal ectoderm or the pre-placodal region (PPR). The PPR subsequently breaks into individual patches of

thickened ectoderm, called placodes, each of which gives rise to a specific subset of cells ranging from neurosecretory cells to sensory neurons to cranial sensory organs. In this review we will discuss what is known about how the PPR is specified, how it is molecularly distinct from the cranial neural crest with which it shares some early features, and how it is subdivided into specific cranial sensory placodes with very different developmental fates.

Cranial sensory placodes and their derivatives

The cranial sensory placodes give rise to several important sensory structures in the vertebrate head (reviewed in LeDouarin et al., 1986; Webb and Noden, 1993; Baker and Bronner-Fraser, 2001; Streit, 2004; Schlosser, 2005, 2010). The most anterior placodes include the single, midline adenohypophyseal placode, and the bilateral olfactory and lens placodes. The adenohypophyseal placode invaginates into the roof of the mouth as Rathke's pouch, and eventually forms the anterior pituitary that contains several types of hormone secreting cells (e.g., somatotropin, prolactin, gonadotropins, thyrotropins, and corticotropins). The olfactory placodes form just lateral to the adenohypophyseal placode, and invaginate as pits that eventually line parts of the nasal cavity as the olfactory sensory epithelium. This tissue

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produces supporting cells, basal stem cells and the primary sensory neurons that project to the olfactory bulbs of the fore-brain. In some animals, a separate domain of the olfactory placode forms the vomeronasal organ, which is specialized for pheromone detection. There is some evidence that other embryonic precursors also contribute to the olfactory sensory epithelium. DiI fate mapping in zebrafish placed olfactory and neural crest precursors in such close apposition as to suggest there may be a neural crest contribution to the olfactory epithelium (Harden et al., 2012). More recently a zebrafish Sox10-GFP reporter line indicated a large neural crest contribution to the microvillus olfactory neurons (Saxena et al., 2013). In mouse, the P0-Cre/EGFP reporter line showed that after birth neural crest contribute to the horizontal basal stem cells (Suzuki et al., 2013). However, neural crest grafts in chick and a different reporter line in mouse do not confirm these observations but instead show that the olfactory ensheath-ing cells are of neural crest origin (Barraud et al., 2010). These different observations raise the issue of whether the reporter constructs unquestionably distinguish between the neural crest and placode precursors (which have a common early developmental program), and whether there are species differences in the embryonic origins of some of the olfactory epithelial cells. Other derivatives of the olfactory placode include neuropeptide- and gonadotropin releasing hormone-secreting neurons that migrate into the forebrain (Murakami and Arai, 1994; Northcutt and Muske, 1994; Hillal et al., 1996; Sabado et al., 2012). The lens placode invaginates as a vesicle in response to signals from the growing optic cup. The anterior layer of the lens vesicle differentiates into lens epithelial cells that provide homeostatic support for the organ and act as stem cells to produce new lens fibers. The posterior layer of the lens vesicle differentiates into highly specialized lens fibers that are filled with transparent crystalline proteins to provide optical clarity.

Separating the anterior and posterior sets of placodes there lie two trigeminal placodes (ophthalmic/profundal and maxillomandibular) on the dorsal and posterior margins of the optic vesicle at the hindbrain level of rhombomere 2. Cells delaminate from these placodes and migrate a short distance to produce the large neurons in the distal parts of the ophthalmic and maxillomandibular lobes of the trigeminal ganglion; neural crest cells migrate adjacent to the placode-derived neurons to contribute the small neurons of the proximal lobes and glia for the entire ganglion. In some species the ophthalmic/profundal ganglion develops as two separate entities (Schlosser and Northcutt, 2000; see also Streit, 2004).

The posterior set of placodes consists of the otic and epibranchial placodes. At the hindbrain level of rhombomere 5 (rhombomere 4 in some species; Ruiz i Altaba and Jessell, 1991), the bilateral otic placodes form. This thickening invaginates as the otic cup, which pinches closed as an otic vesicle. The vesicle undergoes complex morphogenetic movements to form the inner ear (auditory cochlea, vestibular semicircular canals and the otolithic organs [utricle and saccule]), and produces both the structural and neural elements of these organs, as well as the sensory ganglion cells that innervate them. In aquatic species, the lateral line system, which is specialized for detection of water currents and electrical fields, is derived from placodes that surround the otic placode (see Piotrowski and Baker, in this issue). Just anterior and posterior to the otic placode are a series of epibranchial placodes that arise just dorsal to each post-otic branchial/pharyngeal cleft. At the hindbrain level of rhombomere 4, the geniculate placode forms just dorsal to the first branchial/pharyngeal cleft. It gives rise to the large neurons of the geniculate (distal) ganglion of the facial cranial nerve; neural crest gives rise to the small neurons of the proximal facial ganglion and the glia of both ganglia. The paratympanic organ in birds and the spiracular organ

in some fishes are derived from a placode located just dorsal to the geniculate placode (O'Neill et al., 2012). At the hindbrain levels of rhombomeres 6–8, other epibranchial placodes give rise to sensory neurons that delaminate and migrate a short distance to form the large neurons of the distal sensory ganglia of the glossopharyngeal (petrosal ganglion) and vagus (nodose ganglion) cranial nerves. Neural crest cells give rise to the smaller neurons of the proximal ganglia of these nerves as well as the glia for both sets of ganglia. In certain fishes there are additional branchial arches, and thus additional placodes and cranial ganglia. In some species there also are ventrally located hypobranchial placodes of unknown function (Schlosser, 2003). Thus, like the related neural crest, cranial sensory placode cells can give rise to several cell types: neurosecretory cells; forebrain neurons; sensory ganglion neurons; sensory receptor cells; non-neural crystalline producing cells; non-neural supportive cells.

The pre-placodal region (PPR): a common origin for all sensory placodes

The PPR forms at the border between the neural plate and the epidermis

In the later part of the 19th century, the cranial sensory placodes were identified by histological preparations of vertebrate embryos, and described as forming lateral to the cranial portion of the neural tube. Following the movements of the placode and neural crest cells over developmental time showed that both populations contribute to cranial sensory structures. The early histological analyses were remarkable in their ability to identify placode precursors without the aid of molecular markers. Von Kupffer (1895) described two precursor regions in *Petromyzon* (sea lamprey), one that is dorsolateral and one that is ventrolateral. Platt (1896) agreed with this arrangement in *Necturus* (the aquatic salamander or mudpuppy), but determined that these two zones arose from a single band of thickened ectoderm adjacent to the neural folds. Von Kupffer posited that the placodes arise from unspecified epidermis after an interaction with the neural crest affiliated with each cranial nerve, whereas Platt posited that they arise from a defined zone of ectoderm that is distinct from the epidermis (see Knouff, 1935). Analyses of two species of terrestrial salamanders (*Ambystoma*) also observed thickenings in the epidermis prior to the emergence of definitive placodes (Landacre, 1926; Stone, 1922). Initially there was a disagreement over whether these thickenings were placode precursors or simply thickenings caused by the epidermis folding over underlying organs. Stone showed, by experimentally removing these thickenings, that some were indeed placode precursors whereas others were simply tissue folds. In an analysis of carefully staged frog embryos, Knouff (1935) provided extensive evidence that there is a distinct pan-placodal band lying between the neural ectoderm and the epidermal ectoderm to which all placodes can be histologically traced. It is thicker than the epidermal ectoderm and is cytologically more similar to neural than epidermal cells. Although fate mapping studies in chick (Couly and LeDouarin, 1987, 1990; Streit, 2002) and in several amphibians (reviewed in Schlosser and Ahrens, 2004; Streit, 2004; Pieper et al., 2011) also indicate that all placodes originate from a narrow band surrounding the neural plate; Knouff's histologically identified pre-placodal band may not accurately represent the PPR because it extends into the trunk and it only partially coincides with the domains of PPR molecular markers (Schlosser and Ahrens, 2004; Litsiou et al., 2005). Nonetheless, similar histological studies in several vertebrates, as well as the expression of common sets of molecular markers (discussed in the section Molecular identity of the PPR) support the idea that