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Sensational placodes: Neurogenesis in the otic and olfactory systems

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ABSTRACT

For both the intricate morphogenetic layout of the sensory cells in the ear and the elegantly radial arrangement of the sensory neurons in the nose, numerous signaling molecules and genetic determinants are required in concert to generate these specialized neuronal populations that help connect us to our environment. In this review, we outline many of the proteins and pathways that play essential roles in the differentiation of otic and olfactory neurons and their integration into their non-neuronal support structures. In both cases, well-known signaling pathways together with region-specific factors transform thickened ectodermal placodes into complex sense organs containing numerous, diverse neuronal subtypes. Olfactory and otic placodes, in combination with migratory neural crest stem cells, generate highly specialized subtypes of neuronal cells that sense sound, position and movement in space, odors and pheromones throughout our lives.

Introduction

The vertebrate ear and nose share interesting similarities as well as important differences in their modes of sensation. Both sensory systems can detect a vast array of distinct environmental stimuli: the human nose can detect up to 400,000 different odors (Mori et al., 2006), while the inner ear can distinguish a wide range of sounds by amplitude, quality and frequency, and detect different vestibular stimuli (gravity, and linear and angular acceleration). However, the strategies employed by the nose and the inner ear differ significantly regarding the modes of transmission to the brain and discrimination between distinct inputs. Whereas olfactory sensory neurons (OSNs) are primary sensory receptor cells, with axons that project directly to the olfactory bulb, hair cells of the inner ear are secondary sensory receptor cells, lacking an axon. Hair cells convey sound and balance information to the brain indirectly via afferent auditory and vestibular neurons in the VIIIth ganglion (ganglion of the VIIIth (statoacoustic) cranial nerve) (Fig. 1A and B). For the purposes of this review, we will consider both otic neurons and sensory hair cells as neuronal cell types, and use the terms neurogenesis and sensorigenesis, respectively, to describe their generation. Otic and olfactory neurogenesis are highly similar processes, each following a sequence of commitment to a neural fate, initiation of neurogenic divisions to generate neuronal precursors and differentiation via the expression of bHLH genes.

In the olfactory system, sensory neurons are specialized to each detect a single odorant. In the mouse, for example, there are 1200 distinct odorant genes, with generally only one (or a few) expressed by each OSN, thus determining the cell's spectral response (Buck and Axel, 1991). No such receptor specificity exists in the inner ear hair cells. Instead, mechanical forces displace specialized stereociliary bundles such that deflection of the bundles opens ion channels that modulate the cells' membrane potential (Corey, 2009). In the ear, sensory epithelia responsible for detection of auditory and vestibular inputs are segregated into distinct compartments, and along the mammalian cochlea, differences in frequency sensitivity generate a tonotopic map that in turn is transmitted to the brain. Here, we review current knowledge of the process of development of the olfactory and otic systems, describing their common traits and highlighting their interesting differences, particularly with respect to neurogenesis. We also refer the reader to a number of previous excellent reviews (Fritzsch et al., 2006a, 2006b, 2010; Kelley, 2006b, 2006a, 2009; Sanchez-Calderon et al., 2007; Alsina et al., 2009; DeMaria and Ngai, 2010; Gokoffski et al., 2010; Treloar et al., 2010; Bazáes et al., 2013; Miyasaka et al., 2013; Rodriguez, 2013).

Origin of olfactory and otic placodes

In vertebrates, all peripheral sensory neurons arise from two specialized regions of ectoderm that form at the border of the

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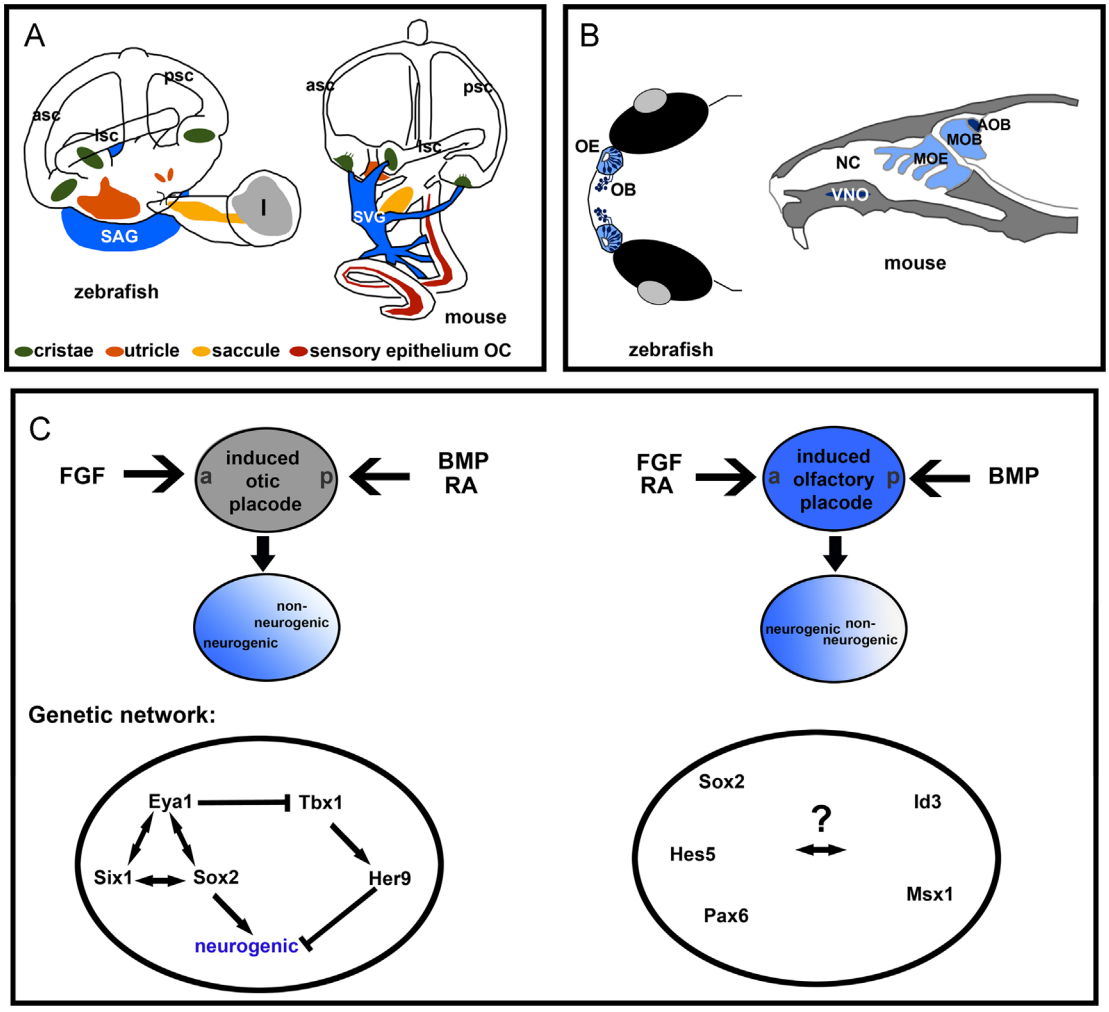

Fig. 1. (A) Schematic drawing of an adult zebrafish and mouse inner ear, their sensory patches and approximate position of the VIIIth ganglion (SAG). (B) Schematic drawing of the olfactory system in an adult zebrafish (dorsal view) and mouse (lateral view; sagittal section). (C) Signals and genetic networks involved in the establishment of the neurogenic region in the otic (left) and olfactory (right) placode during development. Abbreviations: a: anterior, AOB: accessory olfactory bulb, asc: anterior semicircular canal, l: lagena, lsc: lateral semicircular canal, MOE: main olfactory epithelium, MOB: main olfactory bulb, NC: nasal cavity, OB: olfactory bulb, OC: organ of Corti in the cochlea, OE: olfactory epithelium, p: posterior, psc: posterior semicircular canal, SAG: statoacoustic ganglion (VIIIth ganglion), SVG: spiral and vestibular ganglia (VIIIth ganglion), and VNO: vomeronasal organ.

neural plate: the cranial placodes and the neural crest. Placodes are regions of condensed ectoderm arising in the head region that give rise to both non-neural (lens and adenohypophyseal placodes) and neural structures. The neurogenic placodes include the olfactory, trigeminal, profundal, lateral line, otic and epibranchial placodes (Schlosser, 2010). Most neurogenic placodes give rise solely to sensory neurons and associated structures. By contrast, the olfactory and otic placodes give rise to both neural and non-neural structures in the nose and the inner ear, respectively. Moreover, throughout development, both organs undergo a series of cellular rearrangements that spatially distribute their emerging cell types in precise anatomical positions.

Development of the placode-derived sensory organs is a multi-step process. It starts with subdivision of the embryonic ectoderm into epidermal ectoderm, neural ectoderm and the neural plate border region, as reviewed in Groves and LaBonne (this issue). While anterior placodal cells (e.g. olfactory, adenohypophyseal, and lens) express *Six3*, *Pax6* and *Otx2* and emerge in the late gastrula (Ahrens and Schlosser, 2005; Sjödal et al., 2007), posterior placodal cells (e.g. otic and epibranchial) express *Irx3*, *Pax2* and *Gbx2*, and emerge later at the neurula stage in the lateral posterior neural border (reviewed in Schlosser (2006)). Thus, induction of olfactory and otic placodes occurs at different time points and locations in the early embryo. After induction, both olfactory and otic placodes invaginate (or cavitate in zebrafish), transforming from a thickened sheet of ectoderm into a pit and then an epithelial vesicle that is initially a single cell layer thick. Subsequently, the olfactory and otic epithelia transform into multi-layered structures and undergo neurogenesis. The otic placode must undergo further extensive morphogenesis to give rise to the semicircular canal ducts and sensory chambers of the inner ear.

Early establishment of neural competence and a neurogenic domain

During placodal development, a critical first step is the delineation of neurogenic versus non-neurogenic domains in the emerging placode. Several models for placode induction and acquisition of neurogenic competence have been discussed in the literature. One possibility is that induced placodes are inherently neurogenic. Alternatively, there may be a more general neurogenic inductive event, followed by restriction or independent specification of neurogenic and non-neurogenic fates. Interestingly, regardless of the sequence of events, similar underlying molecular programs are involved in both the otic and olfactory placodes (Fig. 1C).