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Signaling mechanisms controlling cranial placode neurogenesis and delamination

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ABSTRACT

The neurogenic cranial placodes are a unique transient epithelial niche of neural progenitor cells that give rise to multiple derivatives of the peripheral nervous system, particularly, the sensory neurons. Placode neurogenesis occurs throughout an extended period of time with epithelial cells continually recruited as neural progenitor cells. Sensory neuron development in the trigeminal, epibranchial, otic, and olfactory placodes coincides with detachment of these neuroblasts from the encompassing epithelial sheet, leading to delamination and ingression into the mesenchyme where they continue to differentiate as neurons. Multiple signaling pathways are known to direct placodal development. This review defines the signaling pathways working at the finite spatiotemporal period when neuronal selection within the placodes occurs, and neuroblasts concomitantly delaminate from the epithelium. Examining neurogenesis and delamination after initial placodal patterning and specification has revealed a common trend throughout the neurogenic placodes, which suggests that both activated FGF and attenuated Notch signaling activities are required for neurogenesis and changes in epithelial cell adhesion leading to delamination. We also address the varying roles of other pathways such as the Wnt and BMP signaling families during sensory neurogenesis and neuroblast delamination in the differing placodes.

Introduction

Cranial placodes are a unique model of neural development. In vertebrate embryos neurons are generated from three sources, the neuroepithelium of the neural tube, the neural crest, and the ectodermal cranial placodes. Placodes share the epithelial characteristic of the CNS neuroepithelium and the transient migratory nature of the neural crest. Cranial placodes arise from a preplacodal domain of ectodermal progenitor cells. After initial induction of this panplacodal primordium into individual placodes, each placode is specified for a unique sensory fate. While some placodes contribute non-neuronal cell types to cranial sensory organs, the neurogenic placodes that contribute sensory neurons to the PNS include the trigeminal, epibranchial, otic, and olfactory placodes. Placode-derived neurons enter the mesenchyme to comingle with neural crest cells to establish cranial ganglia, the sensory nervous system component of cranial nerves. A recent study highlighted the important interactions of neural crest and placode cells in this process (Freter et al., 2013). Two key cellular processes early in placodal sensory neuron development are: (1) neuronal determination, where primed progenitor epithelial cells are selected for a neuronal fate, undergoing neurogenesis and neuronal differentiation; and (2) delamination from the epithelium, whereby cells detach from their epithelial neighbors and escape through breaks in the basement membrane into the mesenchyme as migratory sensory neuroblasts in a process different from the epithelial to mesenchyme transition (EMT) seen in neural crest cells (Graham et al., 2007).

In this focused review we will only briefly introduce the neurogenic placodes, and then comprehensively examine how the Notch, FGF, Wnt, and BMP signaling protein families direct sensory neurogenesis and delamination from the placodal epithelium, where the pathways are conserved, where they diverge, and what we still have to learn about the differentiation process.

Origins and derivatives of neurogenic placodes

Progenitors within the neurogenic placodes give rise to different types of sensory neurons/cells, which contribute to the cranial

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ganglia, the inner ear, and the olfactory epithelium. Sensory neurons originating from the placodes delaminate from the epithelium, migrate and condense to form the cranial ganglia. The sole derivatives of both the trigeminal and epibranchial placodes are sensory neurons of the cranial ganglia (D'Amico-Martel and Noden, 1983; Harlow and Barlow, 2007). The neural contribution of the otic placode includes both secondary sensory hair cells of the inner ear and sensory neurons of the cochleovestibular ganglion (CVG), which delaminate from the epithelium of the invaginated otic vesicle. The neurogenic portion of the olfactory placode gives rise to delaminating neurons in the migratory mass and chemosensory receptor neurons, the latter remain in the olfactory epithelium (Beites et al., 2005; Kawauchi et al., 2004).

Trigeminal placode

While some of the cranial placodes produce cell types other than neurons, sensory neurons are the sole derivative of the trigeminal placodes. The trigeminal placode consists of two molecularly distinct sub-placodes, the ophthalmic (opV) and the maxillomandibular (mmV). The opV and mmV placodes each contribute neurons to the distal region of their respective ganglionic lobes, while the neural crest contributes proximal neurons, as well as glial cells (Baker and Bronner-Fraser, 2000, 2001; D'Amico-Martel and Noden, 1983; Schlosser, 2006). The trigeminal ganglion, the sensory ganglion of cranial nerve V, is the largest of the cranial ganglia and provides sensation to much of the face and jaw. Trigeminal ganglion neurons are primary sensory neurons, responsible for touch, pain, and temperature sensation from the head.

Fate mapping studies in the chick have shown that the opV placode develops in the ectoderm adjacent to the midbrain and the midbrain-hindbrain boundary (MHB), while the mmV placode is found directly caudal at the rhombomeres 2 & 3 level (Xu et al., 2008). In both chick and mouse, trigeminal neurons first develop in the opV placode followed by the mmV placode, while neural crest-derived neurons differentiate at considerably later stages (Covell and Noden, 1989; d'Amico-Martel and Noden, 1980; Moody et al., 1989a, 1989b; Nichols, 1986; Stainier and Gilbert, 1991; Verwoerd et al., 1981).

Epibranchial placodes

Similar to the trigeminal placode, epibranchial placodes give rise solely to sensory neurons of the cranial ganglia; they are located at the hindbrain axial level and develop ventral to the otic placode in the dorsal and caudal margins of the pharyngeal clefts (Begbie et al., 2002, 1999; Graham et al., 2007; Ladher et al., 2010). The epibranchial placodes consist of the geniculate, petrosal, and nodose placodes which produce neuroblasts in the surface ectoderm that delaminate and migrate, contributing viscerosensory neurons to cranial nerves VII (facial), IX (glossopharyngeal) and X (vagus), respectively, innervating several visceral organs and the taste buds (Northcutt, 2004).

Otic placode

The otic placode gives rise to the entire inner ear, including the sensory hair cells and the innervating sensory neurons of the CVG (Torres and Giraldez, 1998). Each otic placode is located adjacent to rhombomeres 5 and 6 of the posterior hindbrain, and this oval sheet of thickened placodal epithelium invaginates, forming the otic cup, which subsequently closes and detaches from the surface ectoderm as it becomes the otic vesicle. The otic vesicle undergoes continued morphogenesis during early development, ultimately producing all of the structures of the inner ear. The CVG develops from neuroblasts in the otic epithelium that delaminate and migrate from the neurosensory domain of the otic vesicle, and also from a contribution of neural crest cells which differentiate to glial cells (Barald and Kelley, 2004; Carney and Silver, 1983; D'Amico-Martel and Noden, 1983; Rubel and Fritzsch, 2002; Schneider-Maunoury and Pujades, 2007). Progenitors in the neurosensory domain of the otic vesicle appear to be able to differentiate as sensory neurons, hair cells, and supporting cells, making it a more complex model for sensory neurogenesis. Neural crest cells have recently been described as contributing more broadly, first integrating themselves into the otic epithelium, and then differentiating alongside placode-derived cells (Freyer et al., 2011).

Olfactory placode

The olfactory placode, like the otic, invaginates to form the olfactory pit and generates migrating cells including the neuropeptidergic neurons, such as GnRH-secreting neurons that eventually enter into the forebrain and contribute to the neuroendocrine compartments (Tarozzo et al., 1995). Different from other neurogenic placodes, the olfactory placode also gives rise to a dominant group of sensory neurons, the olfactory sensory cells, which do not delaminate from the placode and reside within the olfactory sensory neuroepithelium to transduce odor and pheromone signals to the CNS through their projection axons (the olfactory nerve) (Croucher and Tickle, 1989). Additional cell types derived from the olfactory placode include the basal progenitors and the non-neuronal sustentacular cells residing in the olfactory epithelium, and in a classic view, also include the olfactory ensheathing cells (OECs) which delaminate from the olfactory epithelium to the lamina propria and ensheath the olfactory axons. However, the origins of OECs have recently been challenged by several genetic fate mapping studies as they are likely derived from the neural crest cells (reviewed by Forni and Wray, 2012). Nevertheless, neuronal cells delaminating from the olfactory placodal epithelium are consistent with the properties of delaminating sensory neuroblasts that contribute to cranial ganglia from the other neurogenic placodes.

Signaling pathways critical in placode neurogenesis and delamination

Neurogenic placodes continuously generate neuroblasts within the epithelium over an extended period of time, indicating that the placodes represent specialized epithelial progenitor niches (Graham et al., 2007). Neurogenesis begins within these restricted zones and the primary morphological event of the placode is delamination of neuroblasts from the specified epithelium (Graham et al., 2007; Lassiter et al., 2010; McCabe et al., 2009). Sensory neurons are derived from both the cranial placodes and the neural crest migratory cell populations; however, placodal delamination differs markedly from that of neural crest. The process of sensory neurogenesis in the placodes also differs somewhat from that observed for neural crest. Neurogenesis begins within the epithelium prior to cells delaminating and becoming migratory. This is evidenced by the expression of early neuronal markers (Ngn, Isl1, NeuroD) and by a significant reduction in cycling cells, although some neuronal precursors are not yet post-mitotic. Identifying differentiating neurons morphologically is only possible as they begin to exit the epithelium, at which time delaminating neuroblasts appear to escape the epithelium individually or in small clusters. In the epibranchial placodes, for example, cells emerge from a pseudostratified single-layered epithelium as neuronal cells with distinct neuronal morphology (Graham et al., 2007). At the site of neuroblast exit from the