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Review

The peripheral sensory nervous system in the vertebrate head: A gene regulatory perspective

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ABSTRACT

In the vertebrate head, crucial parts of the sense organs and sensory ganglia develop from special regions, the cranial placodes. Despite their cellular and functional diversity, they arise from a common field of multipotent progenitors and acquire distinct identity later under the influence of local signalling. Here we present the gene regulatory network that summarises our current understanding of how sensory cells are specified, how they become different from other ectodermal derivatives and how they begin to diversify to generate placodes with different identities. This analysis reveals how sequential activation of sets of transcription factors subdivides the ectoderm over time into smaller domains of progenitors for the central nervous system, neural crest, epidermis and sensory placodes. Within this hierarchy the timing of signalling and developmental history of each cell population is of critical importance to determine the ultimate outcome. A reoccurring theme is that local signals set up broad gene expression domains, which are further refined by mutual repression between different transcription factors. The Six and Eya network lies at the heart of sensory progenitor specification. In a positive feedback loop these factors perpetuate their own expression thus stabilising pre-placodal fate, while simultaneously repressing neural and neural crest specific factors. Downstream of the Six and Eya cassette, Pax genes in combination with other factors begin to impart regional identity to placode progenitors. While our review highlights the wealth of information available, it also points to the lack information on the cis-regulatory mechanisms that control placode specification and of how the repeated use of signalling input is integrated.

Introduction

The sensory placodes give rise to most of the peripheral sensory nervous system in the vertebrate head. They form the lens of the eye, the inner ear and the olfactory epithelium and, together with neural crest cells, contribute to the cranial sensory ganglia. Initially, placodes develop as simple patches of ectoderm outside of the central nervous system, but subsequently produce a large variety of cell types ranging from simple lens fibres to sensory cells and neurons, neuroendocrine cells as well as self-renewing stem cells in the olfactory epithelium. As a defining feature of vertebrates, placodes have recently attracted much attention and the molecular pathways controlling their development are beginning to be unravelled.

Placode formation and differentiation is a long process. One of the most surprising findings is that despite their diversity, placodes arise from a common territory of multipotent precursors, the pre-placodal region (PPR), and their progenitors initially share common properties (Bailey et al., 2006; Martin and Groves, 2006; for review: Schlosser, 2006, 2010; Streit, 2007, 2008)—a hypothesis originally proposed almost 50 years ago (Jacobson, 1963a, b, c; see also Torres and Giraldez, 1998). Placode progenitors are specified from "the border", a region where neural and non-neural gene expression overlaps and where cells are initially competent to give rise to neural, neural crest and placodal derivatives, as well as epidermis (Baker et al., 1999; Basch et al., 2000; Bhattacharyya and Bronner-Fraser, 2008; Gallagher et al., 1996; Gallera and Ivanov, 1964; Groves and Bronner-Fraser, 2000; Hans et al., 2007; Köster et al., 2000; Kwon et al., 2010; Liedke, 1942, 1951; Martin and Groves, 2006; Nieuwkoop, 1958; Pieper et al., 2012; Selleck and Bronner-Fraser, 1995; Servetnick and Grainger, 1991; Storey et al., 1992; Streit et al., 1997; Waddington, 1934, 1935; Waddington and Needham, 1936). Specification of placode progenitors is controlled through a balance of inductive and repressive signals emanating

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from surrounding tissues: the adjacent neural plate and future epidermis and the underlying mesoderm (Ahrens and Schlosser, 2005; Brugmann et al., 2004; Litsiou et al., 2005). Subsequently, placode precursors become different from each other (Ladher et al., 2010; McCabe and Bronner-Fraser, 2009; Ohyama et al., 2007; Schlosser, 2010) and converge from an initially wide distribution within the pre-placodal region (PPR) towards focal thickenings (the placodes) (Bhattacharyya et al., 2004; Pieper et al., 2011; Streit, 2002; Xu et al., 2008). Once formed, placodes either remain as transient neurogenic patches from which neuroblasts delaminate to form the cranial ganglia or expand to deposit neuromasts along the entire body axis, as is the case for the lateral line in amphibians and fish. Alternatively, they invaginate, undergo complex morphogenetic changes and differentiate into various organ-specific cell types characteristic for the lens, otic and olfactory tissues.

Thus, from initial placode progenitor induction to terminal differentiation, ectodermal cells navigate a hierarchy of regulatory states with successively limited developmental potential. Emerging molecular data point to a complex gene regulatory network (GRN) that controls these events and distinguishes placode precursors from other ectodermal derivatives such as the neural plate, neural crest and epidermis. Within this network, each step in the temporal hierarchy can be identified by a specific set of transcription factors (defining the regulatory state of cells at this stage), which cross-regulate each other and which in turn are controlled by defined signalling inputs. While direct interactions and cis-regulatory modules of genes expressed in the placodes are only beginning to be elucidated, there are now sufficient gain- and loss-of-function data to begin to assemble a GRN to model the transition from multipotent placode progenitors towards differentiated placode derivatives. Such networks represent a powerful way to represent developmental processes and cell fate decisions as they allow the integration of large amounts of data into logical circuits (Betancur et al., 2010a; Davidson, 2009; Levine and Davidson, 2005; Peter and Davidson, 2011). For placode development, the main challenge is the integration of information from different animal models that differ in the timing of these events and in the experimental approaches that can be used. Even more complexity arises from the dynamic nature of the process, as illustrated by continuous changes in gene expression and the repeated use of the same signals. Here, we will first provide a brief overview of placode derivatives and their development. Then we will summarise the known molecular events that control the specification of placode progenitor cells and their patterning along the anterior–posterior axis. We will integrate this information into a gene regulatory network using BioTapestry as a tool (Longabaugh et al., 2005, 2009).

Placodes and their derivatives

During embryonic development sensory placodes are first visible as epithelial thickenings next to the developing neural tube (Fig. 1b). Two placodes are non-neurogenic: the adenohypophyseal and lens placodes. While the latter forms next to the future retina to generate the crystalline lens of the eye with lens fibre and epithelial cells, the former develops in the midline and gives rise to the anterior pituitary gland, which generates different neuroendocrine cells. The ophthalmic and maxillomandibular trigeminal placodes (profundal and trigeminal in anamniotes) and epibranchial placodes are simple neurogenic patches, from which neuroblasts delaminate to form the distal portions of the Vth, VIIth, IXth and Xth ganglia. While the trigeminal (Vth) ganglion provides somatosensory innervation from the face, the epibranchial placode-derived neurons provide viscerosensory input from the heart and other visceral organs and gustatory information from the oral cavity. In aquatic vertebrates, the pre- and post-otic lateral line placodes form a specialised sensory system for the detection of water movement and electric fields along the entire body axis generating both neurons and sensory cells. Finally, the otic and olfactory placodes form next to the hindbrain and future olfactory bulb, respectively, and undergo complex tissue reorganisation and folding after their initial invagination. The otic placode forms the auditory and vestibular part of the inner ear including sensory hair cells, the neurons that innervate them, supporting and endolymph-secreting cells, while the olfactory placode produces different cell types including olfactory sensory neurons, stem cells that regenerate them throughout life as well as a variety of migratory neurons that leave the placode to localise in the brain. Placode derivatives have been described in great detail in other recent reviews (Baker and Bronner-Fraser, 2001; Schlosser, 2010); however, this brief summary highlights their diversity in both structure and function (Fig. 1c).

Placode progenitor distribution and their relationship with neighbouring cells

Before and during gastrulation, placode precursors are widely dispersed in the ectoderm and intermingle with future neural, neural crest and epidermal cells (Ezin et al., 2009; Fernandez-Garre et al., 2002; Garcia-Martinez et al., 1993; Hatada and Stern, 1994; Streit, unpublished) and a unique placodal territory cannot be defined. However, shortly after the neural plate is established, placode progenitors co-localise to a contiguous band of ectoderm at its border, the pre-placodal region (PPR; Fig. 1a; Bhattacharyya et al., 2004; Dutta et al., 2005; Kozlowski et al., 1997; Pieper et al., 2011; Streit, 2002; Xu et al., 2008). They continue to be interspersed with other ectodermal derivatives and segregation occurs only after neural fold formation in chick, but slightly earlier in *Xenopus*. Two recent studies in zebrafish and *Xenopus* indicate that a first lineage restriction occurs between neural/neural crest and placode/epidermal lineages due to changes in competence (Kwon et al., 2010; Pieper et al., 2012). Initially, future epidermis is competent to generate neural, neural crest and placode cells; however as development proceeds, competence for neural and neural crest is lost, while placodal competence persists. Conversely, a young neural plate grafted into the border region can be induced to express both neural crest and pre-placodal markers, while an older neural plate has lost competence to produce placode precursors. While these experiments argue for an early restriction of competence in the neural plate and future epidermis, they leave open the possibility that in vivo cells at the border retain plasticity to change their fate depending on local signals.

Within the PPR, precursors for different placodes are initially mixed, but segregate over time to form morphological placodes with unique identities. The degree of overlap is still under debate as is the question of whether cell movements contribute to the separation of different cells with different fates (Bhat and Riley, 2011; Bhattacharyya et al., 2004; Pieper et al., 2011; Streit, 2002; Xu et al., 2008; for review: Schlosser, 2006; Streit, 2008). On one hand, it is possible that fate map data have overestimated the extent of cell mixing for technical reasons (for discussion see Pieper et al., 2011; Schlosser, 2006); on the other hand, species-specific differences may exist that reflect distinct modes of placode formation. While little or no movement is observed in *Xenopus* (Pieper et al., 2011), in fish and chick, placode precursors appear to move extensively although it is not clear whether movement is random or directional (Bhat and Riley, 2011; Bhattacharyya et al., 2004; Streit, 2002). Ultimately, live imaging over long periods will be required to resolve these issues. At this point the question remains of whether cells within the PPR are truly multipotent and acquire different fates according to their final location, or whether cells pre-committed to specific fates segregate