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Review

From classical to current: Analyzing peripheral nervous system and spinal cord lineage and fate

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ABSTRACT

During vertebrate development, the central (CNS) and peripheral nervous systems (PNS) arise from the neural plate. Cells at the margin of the neural plate give rise to neural crest cells, which migrate extensively throughout the embryo, contributing to the majority of neurons and all of the glia of the PNS. The rest of the neural plate invaginates to form the neural tube, which expands to form the brain and spinal cord. The emergence of molecular cloning techniques and identification of fluorophores like Green Fluorescent Protein (GFP), together with transgenic and electroporation technologies, have made it possible to easily visualize the cellular and molecular events in play during nervous system formation. These lineage-tracing techniques have precisely demonstrated the migratory pathways followed by neural crest cells and increased knowledge about their differentiation into PNS derivatives. Similarly, in the spinal cord, lineage-tracing techniques have led to a greater understanding of the regional organization of multiple classes of neural progenitor and post-mitotic neurons along the different axes of the spinal cord and how these distinct classes of neurons assemble into the specific neural circuits required to realize their various functions. Here, we review how both classical and modern lineage and marker analyses have expanded our knowledge of early peripheral nervous system and spinal cord development.

Introduction

The advent of molecular cloning techniques in the early 1980s has led to a "golden age" in developmental biology. Many genes that establish the vertebrate body plan have been identified, frequently by cloning the vertebrate homologues of genes first identified in invertebrates (Nusslein-Volhard and Wieschaus, 1980). The expression patterns of these genes are often extremely informative about their function, and can be used in combination with classical transplantation approaches to follow cell fate in the periphery (Le Douarin, 1982). Moreover, when these genes were restricted to specific classes of neural cells, they become invaluable molecular markers, permitting researchers to unambiguously identify specific populations of neural progenitors, post-mitotic neurons and glia. Such markers can distinguish both between different classes of neural cells and different differentiation states within a class of neural cells, *e.g.* progenitor cells versus post-mitotic neurons. A further discovery that transformed developmental biology in the 1990s was the identification of fluorophores, first Green Fluorescent Protein (GFP) (Chalfie et al., 1994) and then a multitude of color variants (Giepmans et al., 2006), which permit researchers to label specific populations of cells with a fluorescent protein, supplied from a developmentally restricted promoter. Such genetically encoded fluorescent markers greatly simplify live imaging of cellular processes (Kaltschmidt et al., 2000). Thus, the existence of cell-type and differentiation-state specific markers has revolutionized our ability to follow developmental events in real time and determine the basis of neural identity and function. Here, we review what has been learned from these approaches in the PNS and CNS, focusing on the neural crest and developing spinal cord.

Origin of the peripheral nervous system and spinal cord

The vertebrate nervous system arises from the ectoderm, following induction of the neural plate in the gastrulating embryo. During the process of neurulation, the neural plate thickens and invaginates to form the cylindrical neural tube along the rostrocaudal axis of the embryo (Fig. 1A and B). In the head, the neural tube expands to form the brain, whereas it forms the spinal cord in the more caudal regions of the embryo (Fig. 1C). Shortly thereafter, neural crest markers become detectable in the dorsal-most portion of the newly closed neural tube along nearly the entire length of the body axis. Neural

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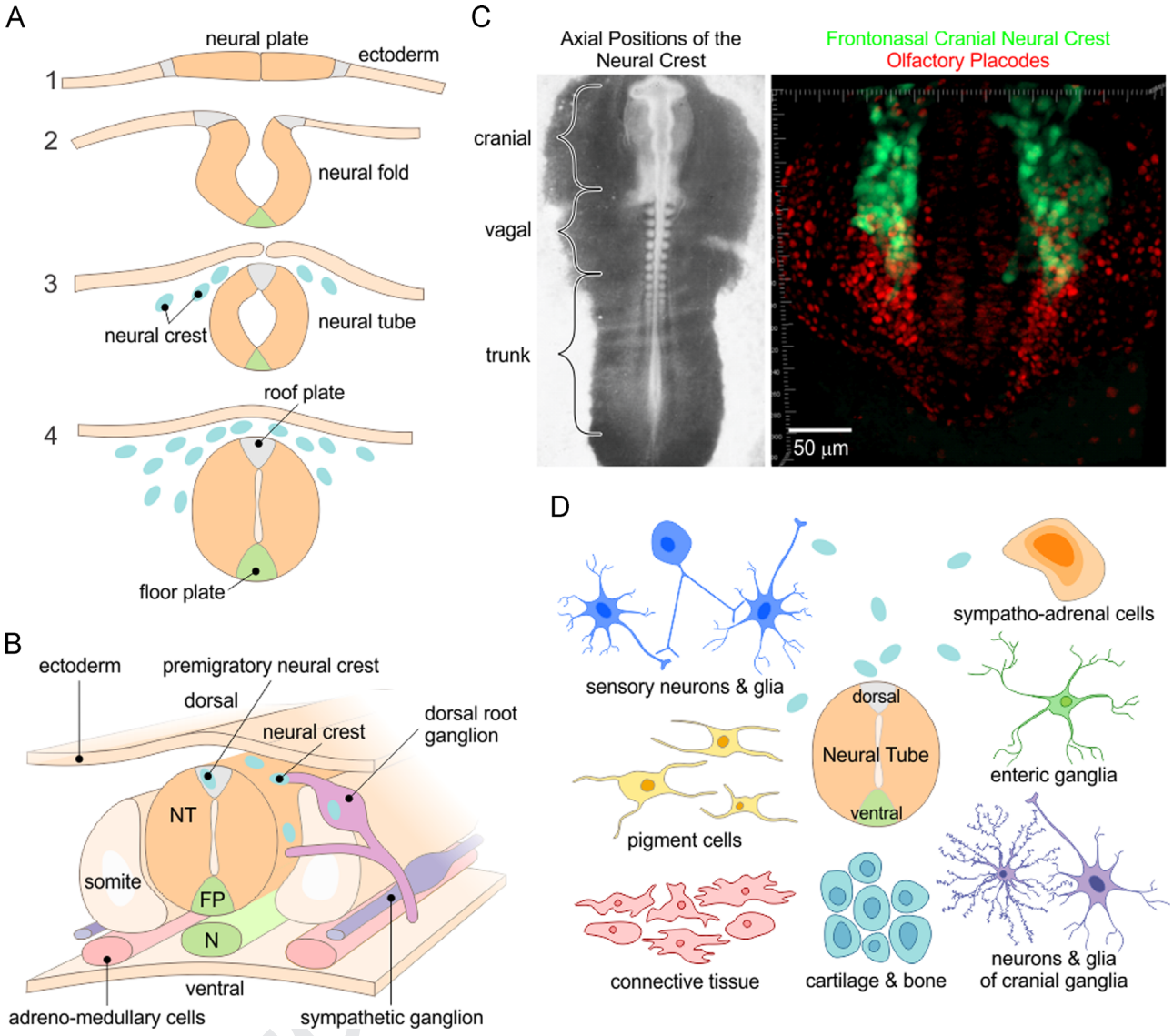

Fig. 1. Formation of the spinal cord and peripheral nervous system. (A) Schematic diagram illustrating the process of neurulation and onset of neural crest migration. (1) Initially, the ectoderm is open and flat. The neural plate thickens in comparison to the adjacent non-neural ectoderm. (2) During neurulation, the neural plate bends and begins to close. (3). Shortly after neural tube closure, neural crest cells emigrate from the dorsal portion of the neural tube and (4) continue migrating into the adjacent mesenchyme. (B) With time, neural crest cells condense to form multiple derivatives, including dorsal root ganglia, sympathetic ganglia, adrenomedullary cells. (C) Different populations of neural crest cells arise from different axial levels of the chicken neural tube. Indicated in this whole mount view of an embryo are the relative sites of emergence of cranial, vagal, trunk and lumbosacral (further caudal but not shown here) neural crest cells. In the adjacent section, cranial neural crest cells expressing Sox10 intermingle with olfactory placode cells in a zebrafish embryo. Both will differentiate into olfactory sensory neurons within the olfactory epithelium. (D) Schematic diagram illustrating some of the diverse derivatives that arise from the neural crest, including PNS neurons and glia, pigment cells, and craniofacial cartilage.

crest cells subsequently undergo an epithelial to mesenchymal transition, delaminate from the neural tube and commence migration to diverse and sometimes distant regions of the embryo (Le Douarin, 1982). Neural crest cells migrate into the periphery and contribute to the PNS, as well as many other derivatives (Fig. 1D), while the neural tube gives rise to the CNS.

At cranial levels, the peripheral nervous system has a dual origin from both cranial neural crest cells and ectodermal placodes (Baker and Bronner-Fraser, 2001; Couly and Le Douarin, 1985; D'Amico-Martel and Noden, 1983). The placodes give rise to cranial sensory ganglia and the sense organs (nose, ears, lens of eye); they are discrete regions of thickened columnar epithelium within the head ectoderm (Webb and Noden, 1993). Most placodes (otic, lateral line, epibranchial) form in the ectoderm adjacent to the neural tube except for the olfactory and adenohypophyseal placodes that originate within the anterior neural folds (Eagleson and Harris, 1990), the only region of the neural tube that does not form neural crest (Fig. 1C).

Further caudally, the entire PNS is derived from neural crest cells. "Vagal" neural crest cells arise from the neural tube just behind the ear and to the level to adjacent to somite 7. These cells migrate extremely long distances to form the enteric ganglia of the gut. This unique portion of the PNS is responsible for gut motility. At trunk levels, neural crest cells contribute to dorsal root and sympathetic ganglia of the PNS. The dorsal root ganglia are sensory and form bilaterally adjacent to the developing spinal cord. They innervate the skin and various organs that sense proprioception, temperature and injury. Other neural crest cells migrate further ventrally to form the sympathetic chain ganglia. These cells innervate numerous organs along the length of the trunk.

At trunk levels, the remainder of the neural tube gives rise to the spinal cord. Initially only a single cell thick, the early neural tube is a pseudostratified epithelium comprised of rapidly dividing cells oriented perpendicular to the lumen of the tube (Fig. 1A) (Altman and Bayer, 1984). These cells are the progenitors for all of

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