SnapShot: Neural Crest

Cell

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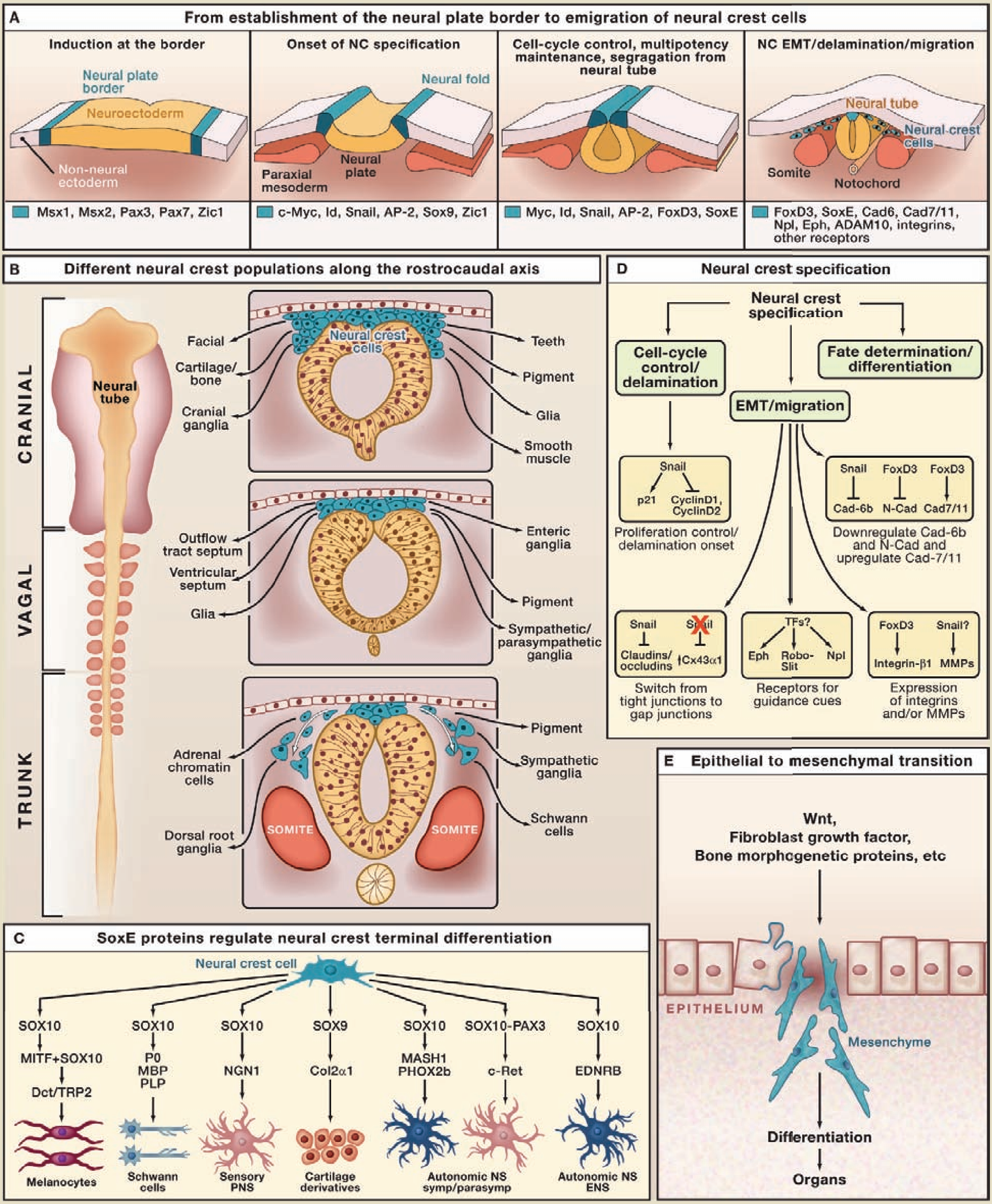

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The neural crest is a transient population of cells that emerges from the neural tube during the early stages of embryonic development. Neural crest cells are unique to vertebrates and have properties similar to stem cells, including the ability to differentiate into many cell types (i.e., multipotency) and to regenerate. Neural crest cells migrate extensively throughout the embryo and then differentiate to give rise to most of the cells in the peripheral nervous system and the facial skeleton. Because of their multipotency and regenerative ability, neural crest cells recently have garnered great attention for their potential use in stem cell-based therapies. In this SnapShot, we describe key regulatory events involved in neural crest formation, differentiation, and migration during early stages of vertebrate development.

Formation of Neural Crest during Neurulation

In the human embryo, the nervous system begins to develop 1 month after fertilization. Following neural induction, a subset of cells in the ectoderm differentiates into neuroectoderm to form the neural plate. The cells in the neural plate eventually give rise to both the central and peripheral nervous systems, including the enteric nervous system (ENS), a portion of the peripheral nervous system (PNS) that controls the gastrointestinal system.

Induction of the neural crest occurs shortly after neural induction at the neural plate border between the neural and non-neural ectoderm (Figure 1A). Transforming into the neural folds, presumptive neural crest cells form the leading edge of the closing neural tube. The neural folds then appose, leading to neural tube closure. Subsequently, neural crest cells undergo an epithelial to mesenchymal transition (EMT), whereby cell-cell interactions are severed to release the cells from their surrounding tissue. This transition allows the neural crest cells to delaminate (i.e., split away) from the neural tube and begin their migration.

Neural Crest Migration

The left side of Figure 1B shows a vertebrate embryo equivalent to ~1 month of human development. Looking down the back of the embryo (i.e., the dorsal view), the head of the embryo is at the top (i.e., anterior or rostral), and the tail is at the bottom (i.e., posterior or caudal). The right side of Figure 1B illustrates transverse sections of the neural tube at different axial levels with the back (i.e., dorsal) side on top and notochord below (i.e., ventral) to the neural tube.

In most vertebrates, neural crest cells emerge from the neural tube (i.e., the presumptive central nervous system) shortly after the tube closes. They then migrate extensively to various locations throughout the embryo, with their destinations depending on the axial level of their origin. For example, neural crest cells emigrating at cranial levels contribute to numerous derivatives, including cranial ganglia and craniofacial skeleton; cells arising at cardiac/vagal levels contribute to portions of the heart, outflow tract, and enteric ganglia; and, cells arising at trunk levels contribute to dorsal root and sympathetic ganglia. Neural crest cells also form pigment cells that arise at all axial levels.

Gene Regulatory Networks Underlying Neural Crest Formation and Migration

Induction of the neural plate border (Figure 1A, left) is mediated by signaling molecules, including Wnts (wingless and int), BMPs (bone morphogenetic proteins), Delta/Notch, and FGFs (fibroblast growth factors). These signals induce a set of transcription factors (TFs) at the neural plate border, called neural plate border specifiers (Figure 1A, middle), which in turn induce another set of transcription factors, called neural crest specifiers. The neural crest specifiers confer to the cell population the ability to migrate and differentiate (Figure 1A, right). This gene regulatory network is comprised of numerous interwined subcircuits.

Neural crest specifiers control a myriad of processes that lead to substantial changes in the adhesive properties, shape, motility, and signaling equipment of neural crest precursor cells. These modifications allow the cells to emigrate from the neural tube but also to respond to cell-cell interactions and environmental cues that influence their migration. These regulators accomplish this enormous task by directly controlling the expression of downstream effector genes.

The Wnt pathway (Figure 1C) is one of the fundamental signaling components at numerous steps of neural crest development and acts in concert with BMPs and FGFs to induce the neural crest in all vertebrates. Specification of the neural plate border requires β-catenin-dependent Wnt signaling (Figure 1A), and Wnt is the essential activating input for the neural plate border specifiers, such as Gbx1, Msx1, Pax3, or Zic1.

Conversely, the manifestation of the migratory phenotype during neural crest specification requires noncanonical Wnt signaling. This is mediated by small Rho GTPases involved in the epithelial to mesenchymal transition (Figure 1E) and neural crest adhesion. As neural crest cells migrate, they translate these guidance cues into cytoskeletal changes through RhoA, which causes dynamic filopodial retraction (and/or extension), assembly of stress fibers, and changes in cell adhesion. These cytoskeletal rearrangements facilitate directional migration through cell-cell and cell-environmental interactions. RhoA and Rac1 influence expression of the neural crest specifier genes *Snail1*, *Snail2*, *Sox9*, *Sox10*, *Id*, and *FoxD3*.

The transcriptional repressor Snail2 (Figure 1C) downregulates expression of cadherins (e.g., Cadherin-6b), molecules often associated with stable epithelial cell populations. In addition, Snail contributes to the dissolution of tight junctions by repressing proteins that constitute the junction's backbone (e.g., Claudin), allowing the cells to segregate from the neuroepithelim. Snail2 also controls the cell cycle by regulating CyclinD or p21.

Conversely, Snail2 is endogenously downregulated in cranial neural crest as they continue their migration. A decrease in Snail2 leads to the expression of genes associated with mesenchymal and migratory phenotypes, such as the gap junction protein connexin-43a1. Snail and FoxD3 also regulate the expression of proteins that control interactions between neural crest and their environment as the cells migrate. Such factors include matrix metalloprotease-2 (MMP2), integrinb1, or cadherin-7 (Cad7).

The Sox10 transcription factor (Figure 1E) is a key regulator of the differentiation of neural crest into neuronal derivatives and melanocytes. In melanocyte precursors (i.e., melanoblasts), SOX10 directly regulates the expression of microphtalmia-associated transcription factor (MITF). Together SOX10 and MITF directly control the expression of dopachrome tautomerase (Dct/TRP2), an enzyme essential for melanin synthesis. In the autonomic nervous system, SOX10 controls the expression of *Mash1* (*Mammalian achaete-schute homolog 1*) and *Phox2b* (*paired-like homeobox 2b*), two key sympathetic regulatory factors. During gliogenesis, SOX10 directly regulates myelin genes that are specific to Schwann cells, such as the *protein zero* (*P0*) gene, *myelin basic protein* (*MBP*), and *proteolipid protein* (*PLP*). In addition, Sox10 controls the expression of the gap junction proteins connexin-32 and connexin-47, which are the main structural elements of PNS myelin. Its paralog, Sox9, regulates cartilage development.

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