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Review

Neural crest migration: Patterns, phases and signals

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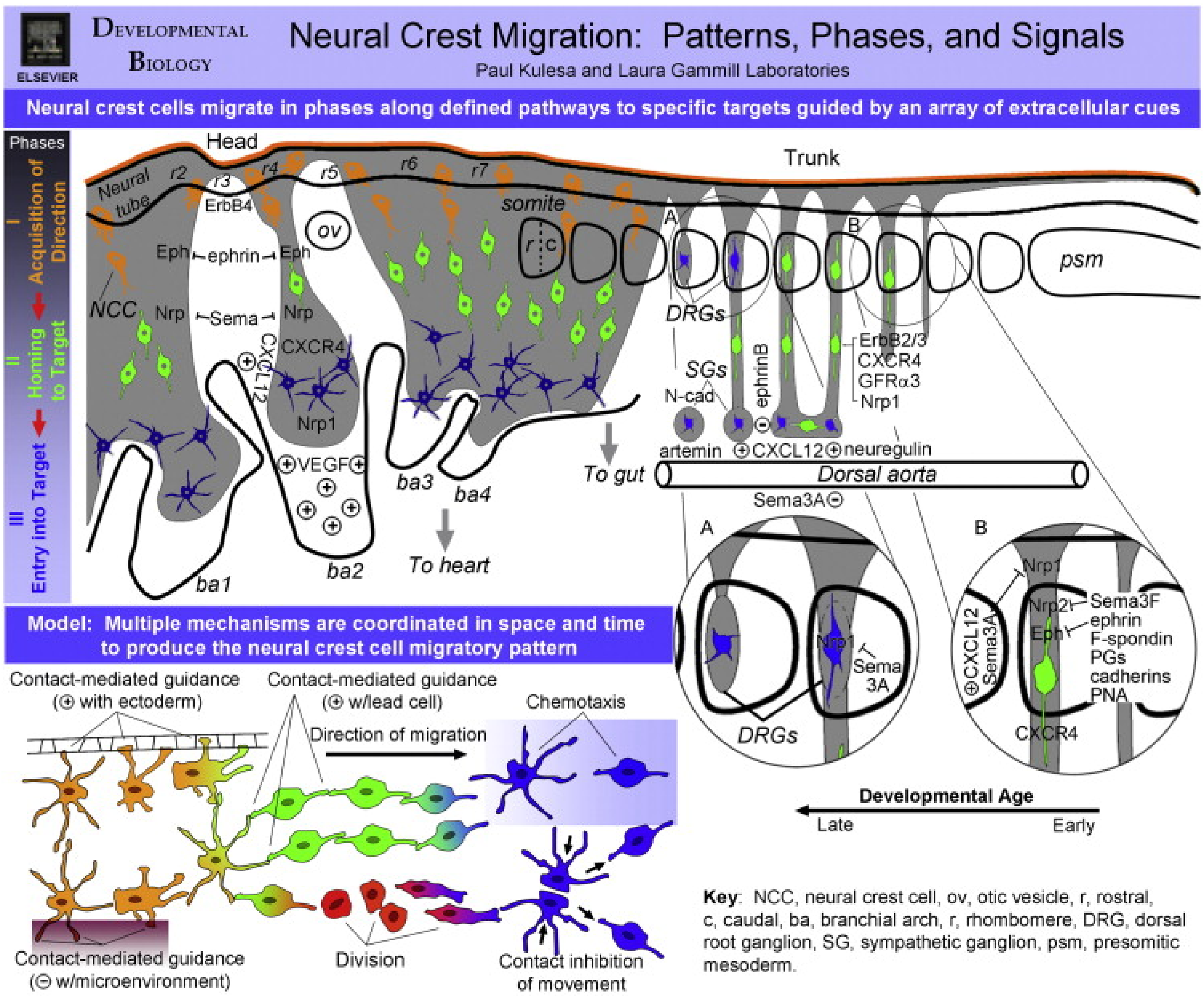

Neural crest cell migration is crucial to head and trunk development

The neural crest is a migratory, multipotent cell type that forms a vast array of vertebrate structures including the craniofacial skeleton and peripheral nervous system (Le Douarin and Kalcheim, 1999). Abnormalities in the ability of neural crest cells to reach precise target sites cause myriad birth defects. Unraveling the mechanisms that generate neural crest migratory patterns is essential to understanding how molecular signals sculpt the migration, morphogenesis, and differentiation of structures during development. Furthermore, neural crest migration resembles cancer metastasis, and insights into the programmed invasion of a highly migratory cell type may yield clues into the unprogrammed events during cancer.

Neural crest cells emerge from the dorsal neural tube (orange line) in a rostrocaudal progression, so that neural crest development is more advanced in the head than in the trunk ("Developmental Age" arrow). Neural crest cells invade surrounding tissues along stereotypical pathways (grey), exhibiting three distinct phases in their migratory behaviors (side bar). This idealized embryo illustrates the patterns, phases, and signals of cranial and trunk neural crest migration in a condensed format (Gammill and Roffers-Agarwal, 2010; Kulesa et al., 2010).

The range of neural crest cell behaviors suggests multiple, complex mechanisms that underlie the migratory pattern

Neural crest cells migrate in three distinct phases that include: contact with the ectoderm and microenvironment leading to acquisition of directed migration (phase I; orange); contact-mediated guidance resulting in homing to the target site (phase II; green); and contact inhibition of movement upon entry into and invasion of the target (head) or colonization of the target site (trunk) (phase III; blue). These phases include a complex range of neural crest cell migratory behaviors, including follow-the-leader chains and contact inhibition of movement, that are observed both in the head and trunk (Carmona-Fontaine et al., 2008; Teddy et al., 2004). Rather than acting as solitary mechanisms, these behaviors take place throughout the migratory streams to coordinate directed migration (Kulesa et al., 2010).

Molecular signaling pathways are shared in the head and trunk

In the head, discrete neural crest cell migratory streams are sculpted and maintained by a combination of local microenvironmental cues that vary for each stream. For example, the cell-free space adjacent to rhombomere 3 (r3) requires the Neuregulin ErbB4 receptor (Golding et al., 2000). Distally, Eph/ephrin, and neuropilin/semaphorin inhibition restrict migration to the 1st and 2nd branchial arch (ba) streams (Gammill et al., 2007; Osborne et al, 2005; Schwarz et al., 2008; reviewed in Kulesa et al., 2010). Directed invasion of ba2 involves neuropilin 1 (Nrp1)/vascular endothelial growth factor (VEGF) and CXCR4/CXCL12 chemoattraction (Olesnicky Killian et al., 2009; McLennan et al., 2010).

In the trunk, neural crest migration is patterned by the somites. Trunk neural crest cells, which initially migrate between the somites, are later repelled from the intersomitic space by Nrp1/semaphorin 3A (Sema3A) signaling (trunk balloon B; Schwarz et al., 2009). Attracted into the somite by CXCR4/CXCL12 signaling, neural crest cells are confined to the rostral sclerotome by Nrp2/Sema3F repulsion, with Eph/ephrin signaling, F-spondin, proteoglycans (PGs), cadherins, and peanut agglutinin (PNA)-binding glycoproteins reinforcing this patterned migration (Gammill et al., 2006; reviewed in Gammill and Roffers-Agarwal, 2010). As development proceeds, Nrp1/Sema3A restricts dorsal root ganglia (DRG) condensation rostrally (trunk balloon A; Roffers-Agarwal and Gammill, 2009).

Neural crest cells are attracted past the somite by CXCR4/CXCL12, ErbB2 and 3/Neuregulin, and GFRα3/artemin signaling, with Nrp1/Sema3A repulsion from surrounding tissues restricting them to the dorsal aorta (reviewed in Gammill and Roffers-Agarwal, 2010). Neural crest cells disperse uniformly along the length of the dorsal aorta and are resegmented by repulsive ephrinB expanding segmentally within the mesoderm (Kasemeier-Kulesa et al., 2006). N-cadherin-mediated adhesion, CXCL12, and artemin signaling result in condensation of individualized, segmental sympathetic ganglia (reviewed in Gammill and Roffers-Agarwal, 2010).

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