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# The neural crest

Roberto Mayor\* and Eric Theveneau

## Summary

The neural crest (NC) is a highly migratory multipotent cell population that forms at the interface between the neuroepithelium and the prospective epidermis of a developing embryo. Following extensive migration throughout the embryo, NC cells eventually settle to differentiate into multiple cell types, ranging from neurons and glial cells of the peripheral nervous system to pigment cells, fibroblasts to smooth muscle cells, and odontoblasts to adipocytes. NC cells migrate in large numbers and their migration is regulated by multiple mechanisms, including chemotaxis, contact-inhibition of locomotion and cell sorting. Here, we provide an overview of NC formation, differentiation and migration, highlighting the molecular mechanisms governing NC migration.

**Key words:** Neural crest cells, Epithelium-to-mesenchyme transition, Cell migration, Chemotaxis, Contact-inhibition of locomotion, Cancer, Neurocristopathies

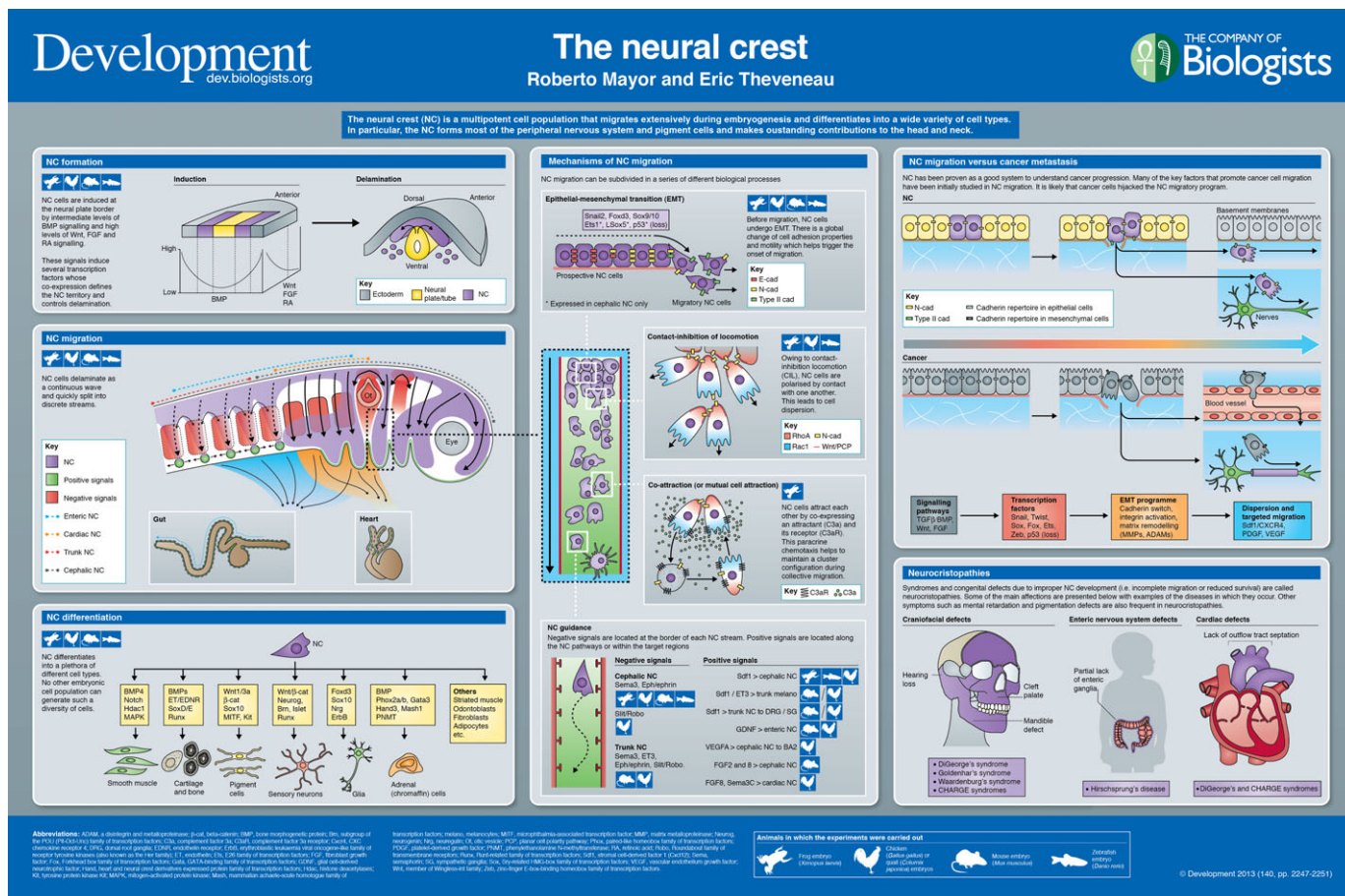
Department of Cell and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK.

\*Author for correspondence (r.mayor@ucl.ac.uk)

## Introduction

The neural crest (NC) is a multipotent stem cell population that is induced at the neural plate border during neurulation and gives rise to numerous cell types. NC cells migrate extensively during embryogenesis using strategies that are reminiscent of those observed during cancer metastasis. Problems in NC development are the basis of many human syndromes and birth defects known collectively as neurocristopathies. The NC population is also a defining feature of the vertebrate phylum. It is responsible for the appearance of the jaw, the acquisition of a predatory lifestyle and the new organisation of cephalic sensory organs in vertebrates. Thus, the NC is a good system for studying cell differentiation and stem cell properties, as well as the epithelium-to-mesenchyme transition (EMT) and cell guidance. As such, NC cells have become an attractive model for developmental and evolutionary biologists, as well as cancer biologists and pathologists.

In this article and in the accompanying poster, we provide an overview of the formation, migration and differentiation of the NC by summarising experimental data obtained in mouse, *Xenopus*, zebrafish and avian embryos. In particular, we highlight the main forces driving NC migration, including the genetic control of EMT,



(See poster insert)

mechanisms of cell cooperation and cell guidance. We then discuss the similarity between NC development and cancer progression to highlight how studying physiological systems such as NC cell migration might provide new insights into cancer cell migration. We finish by presenting some of the developmental defects associated with improper NC development and by proposing future avenues of research for the field.

### Neural crest formation

The NC is induced within the neural plate border region by a precise combination of bone morphogenetic protein (BMP), Wnt, fibroblast growth factor (FGF), retinoic acid and Notch signals produced by the ectoderm, the neuroepithelium and the underlying mesoderm (Milet and Monsoro-Burq, 2012; Prasad et al., 2012). Together, these signals activate the expression of a series of transcription factors, such as those encoded by the *Snail/Slug*, *Foxd3* and *SoxE* genes, that define the NC territory and control subsequent NC development (Cheung et al., 2005; McKeown et al., 2013; Theveneau and Mayor, 2012).

Are NC cells committed to a specific lineage soon after induction or do they remain uncommitted and become progressively restricted while migrating? Despite intense scrutiny, there is still some controversy as to the extent of the multipotency of the NC. Although experimental data suggest that the vast majority of NC cells are not predetermined and differentiate as a result of the signals that they encounter in their environment during migration, some NC cells do seem precommitted to a specific lineage before the onset of migration (Krispin et al., 2010; McKinney et al., 2013). Thus, the NC population appears to be a heterogeneous group composed of cells with various degrees of multipotency and plasticity. Many of the early NC genes that are upregulated at the time of induction also control the EMT that kick-starts migration. Interestingly, EMT has been linked to the acquisition of stem cell properties (Chang et al., 2011; Mani et al., 2008; Morel et al., 2008). This raises the intriguing possibility that NC multipotency and the onset of NC migration might be linked and simultaneously controlled as part of an EMT programme.

### Neural crest derivatives

After migration, NC cells differentiate into an astonishing list of derivatives (Dupin et al., 2006; Hall, 2008; Le Douarin and Kalcheim, 1999; Le Douarin et al., 2012; Theveneau and Mayor, 2011). Cephalic NC cells, which arise from the diencephalon to the third somite, make a vast contribution to craniofacial structures by producing the bones and cartilages of the face and neck as well as tendons, muscles and connective tissues of the ear, eye, teeth and blood vessels. They also form pigment cells and most of the cephalic peripheral nervous system (PNS) and modulate brain growth and patterning. A subpopulation of cephalic NC cells, called the cardiac NC, emerges from the otic level to the anterior limit of somite 4. It migrates to the heart and is essential for the septation of the outflow track. Trunk NC cells, which arise caudal to the fourth somite, form pigment cells, the dorsal root and sympathetic ganglia of the PNS, and endocrine cells of the adrenal gland. Finally, the enteric NC cells delaminate from the neural tube facing somites 1 to 7 and colonise the entire gut to form the enteric PNS, which controls the digestive track.

### Molecular mechanisms of neural crest cell migration

#### Epithelium-to-mesenchyme transition

NC cell migration begins with a complete or partial EMT, which allows NC cells to separate from the neuroepithelium and the

ectoderm (Duband, 2010; Theveneau and Mayor, 2012). A global switch from E-cadherin (cadherin 1) to N-cadherin (cadherin 2) expression occurs at the time of neural induction (Dady et al., 2012; Nandadasa et al., 2009) and thus neural plate and all pre-migratory NC cells express high levels of N-cadherin, with some residual levels of E-cadherin mostly found in the cephalic region. This is followed by another switch, from high to low N-cadherin expression, together with the *de novo* expression of weaker type II cadherins (6/7/11). This is controlled by *Snail/Slug*, *Foxd3* and *Sox9/10* in trunk NC cells (Cheung et al., 2005; McKeown et al., 2013), whereas in the head additional factors such as *Ets1*, *LSox5* and p53 are required (Perez-Alcala et al., 2004; Rinon et al., 2011; Theveneau et al., 2007). In addition, NC cells also express some proteases that are capable of cleaving cadherins such as ADAM10 and ADAM13, further modulating the cell-cell adhesion properties of emigrating NC cells (McCusker et al., 2009; Shoal et al., 2007). These changes, together with a change of integrin activity and local remodelling of the extracellular matrix (ECM), trigger NC migration.

#### Contact inhibition of locomotion

Throughout migration, NC cells retain the expression of some cell-cell adhesion molecules and these are sufficient to mediate transient cell-cell contacts. The most obvious manifestation of these transient contacts is contact-inhibition of locomotion (CIL). CIL is a complex process during which migratory cells momentarily stop upon physical contact with one another and subsequently repolarise in the opposite direction (Mayor and Carmona-Fontaine, 2010). This phenomenon was first described in the 1950s (Abercrombie and Heaysman, 1953) and, in the 1980s, was proposed to act as a driving force for NC cell migration (Erickson, 1985). This idea was further reinforced following observations of NC cell behaviour upon collision *in vitro* and *in vivo* using chick trunk and cephalic NC cells (Rovasio et al., 1983; Teddy and Kulesa, 2004). Overall, CIL prevents cells from overlapping by inhibiting cell protrusions at the site of physical contact. In addition, CIL favours dispersion by actively repolarising cells away from the region of interaction.

The molecular effectors of CIL in NC cells, and its relevance for *in vivo* NC cell migration, have been identified using *Xenopus* and zebrafish cephalic NC cells (Carmona-Fontaine et al., 2008; Theveneau et al., 2010). Transient contacts between two colliding NC cells involve N-cadherin and lead to a local activation of the non-canonical Wnt/planar cell polarity (PCP) pathway, which in turn activates the small GTPase RhoA and inhibits Rac1, thus repolarising the cell. A role for Wnt/PCP in trunk NC cell migration has also been found in chick, zebrafish and mouse, but its connection with CIL has not been analysed (Banerjee et al., 2011; Rios et al., 2011).

#### Co-attraction

Despite experiencing CIL when colliding with one another, NC cells tend to migrate in large groups, following each other and dispersing much less than the effect of CIL would predict. Interestingly, studies in *Xenopus* showed that cephalic NC cells secrete the complement factor C3a and express its receptor C3aR at their surface (Carmona-Fontaine et al., 2011). C3a acts as a chemoattractant and mediates a phenomenon termed co-attraction. A large group of NC cells produces a large amount of C3a, establishing a local gradient. When a cell leaves the migratory NC stream to which it belongs, it is quickly attracted back to it via C3a-dependent chemotaxis. C3aR signalling activates Rac1, which is sufficient to polarise the escaping NC cells toward the bulk of migratory NC cells (Carmona-Fontaine

et al., 2011; Theveneau and Mayor, 2013). This co-attraction phenomenon allows collective migration of NC in spite of low cell-cell adhesion and dispersion induced by CIL. Detailed analyses of migratory NC cells in chick and zebrafish have shown signs of co-attraction-like behaviour, but this behaviour, and its molecular effectors, are yet to be investigated in these models.

### Neural crest guidance

NC migration relies on available permissive ECM, mostly comprising fibronectin, laminins and some collagens, which line the migration routes (Perris and Perissinotto, 2000). Further patterning of NC cells into distinct streams and their precise targeting to specific tissues are controlled by a plethora of negative and positive guidance cues (Alfandari et al., 2010; Kelsh et al., 2009; Kirby and Hutson, 2010; Kulesa et al., 2010; Kuo and Erickson, 2010; Kuriyama and Mayor, 2008; Sasselli et al., 2012; Theveneau and Mayor, 2012).

In the head, delaminating NC cells are forced to assemble into three main subpopulations, mostly by avoiding class 3 semaphorins secreted by the surrounding tissues (i.e. the otic vesicle and adjacent rhombomeres, the eye). Eph/ephrin signalling is also involved. For instance, migratory NC cells with non-compatible Eph/ephrin codes cannot migrate alongside one another and therefore end up in different streams. Similarly, migratory NC cells can only invade a tissue that expresses a compatible Eph/ephrin profile. Further control is endowed by positive guidance cues such as stromal cell-derived factor 1 (Sdf1; also known as Cxcl12), vascular endothelium growth factor (VEGF), FGFs and glial cell-derived neurotrophic factor (GDNF). Sdf1 is required for overall cephalic NC migration in *Xenopus* but its inhibition has only a localised effect on zebrafish NC cells (Olesnicky Killian et al., 2009; Theveneau et al., 2010). In the mouse, FGF2 and FGF8 have been found to control NC migration towards the branchial arches (Kubota and Ito, 2000; Trokovic et al., 2005), while in chick an equivalent role has been described for VEGFA (McLennan et al., 2010). Also in chick, cardiac NC cells seem to rely on FGF8 and semaphorin 3C (here acting as a positive cue) to reach the heart (Lepore et al., 2006; Sato et al., 2011). Finally, data from chick and mouse have demonstrated that GDNF controls enteric NC rostrocaudal progression along the gut to form the enteric nervous system (Sasselli et al., 2012; Young et al., 2001).

Trunk NC cell migration is divided into two alternative paths (Kelsh et al., 2009; Kuo and Erickson, 2010): a dorsolateral pathway that is mostly used by NC cells of the pigment cell lineage, and a ventromedial route used by NC cells forming the trunk PNS. Admittance into the dorsolateral route is mostly controlled by endothelin and Eph/ephrin signalling. In mice, further targeting of melanocytes to the hair follicle is then controlled by Sdf1 (Belmadani et al., 2009). NC cells following the ventral path are restricted to discrete streams by signals produced by the paraxial mesoderm (somites). Only a given region of the mesoderm is permissive for NC cell migration. In chick and mouse, NC cells invade the anterior part of the somites, whereas in fish and frog they migrate adjacent to the middle and posterior part of the somites, respectively. The signals involved in patterning ventral trunk NC cell migration in fish and frogs remain elusive, but studies in chick and mouse embryos have implicated class 3 semaphorins, Eph/ephrins and several ECM components, such as versicans, in preventing migration through the caudal part of each somite (Gammill and Roffers-Agarwal, 2010; Kuo and Erickson, 2010; Kuriyama and Mayor, 2008; Perris and Perissinotto, 2000; Theveneau and Mayor, 2012). In addition, the migration of NC cells

to the anlagen of the sympathetic ganglia in chick and to the dorsal root ganglia in mouse is regulated by Sdf1 (Belmadani et al., 2005; Kasemeier-Kulesa et al., 2010).

Interestingly, cell guidance seems to depend, at least partially, on the fact that NC cells are able to cooperate via transient cell-cell interactions and communications. Indeed, response to semaphorin signalling in cephalic mouse NC cells requires N-cadherin and connexin 43 (also known as Gja1) (Xu et al., 2006; Xu et al., 2001). Similarly, studies in *Xenopus* have shown that CIL mediated by N-cadherin is required for chemotaxis towards Sdf1 (Theveneau et al., 2010). These observations suggest that cell-cell interactions and cell guidance by gradients of secreted molecules are integrated to control cell polarity and regulate directionality over time.

### Neural crest as a model for cancer metastasis

Similar to many tumours, the NC population is heterogeneous and versatile. Both NC cells and cancer cells are known to migrate as solitary cells or collective groups, relying on chemotaxis and metalloproteinases, as well as interaction with their surrounding tissues. Furthermore, numerous signalling pathways and transcription factors involved in NC development have been found to be instrumental in cancer progression, suggesting that some tumours might recapitulate part of NC development in a dysregulated manner (Duband, 2010; Kerosuo and Bronner-Fraser, 2012; Lim and Thiery, 2012; Theveneau and Mayor, 2012; Thiery et al., 2009).

NC development therefore represents a good model with which to study the evolution of a large, heterogeneous and invasive cell population over time. In particular, NC development offers a reproducible and predictable *in vivo* model that can be used to investigate the three key features of cancer metastasis: EMT, invasion, and long-distance cell migration (Hanahan and Weinberg, 2011). NC cells are a particularly good model for NC-derived tumours such as melanoma (skin cancer) and neuroblastoma (derived from sympathetic NC precursors, often arising from one of the adrenal glands). For instance, in these two tumours, cell migration and targeting to distant tissues involve N-cadherin and Cxcr4-dependent chemotaxis (Bonitsis et al., 2006; Nguyen et al., 2009). Furthermore, numerous tumours spread along nerves in a process known as perineural invasion. Upregulation of N-cadherin in cancer cells favours perineural invasion, and during development Schwann cell precursors from the NC also rely on N-cadherin to interact with growing nerves (De Wever and Mareel, 2003; Wanner et al., 2006), thus providing an interesting model with which to study the role of nerves as support for cell migration. Finally, many tumours, such as gliomas, are known to secrete growth factors and their cognate receptors (Hoelzinger et al., 2007). Some, like VEGFs and FGFs, can act as attractants. Thus, it is possible that some tumours might use these factors not only for growth and survival but also to maintain cell density and promote cooperation, as recently shown in *Xenopus* cephalic NC cells via C3a/C3aR signalling.

### Neurocristopathies

NC development has been of interest to pathologists because numerous congenital birth defects, such as the DiGeorge, Treacher-Collins and CHARGE syndromes or Hirschsprung's disease, are due to improper NC development (Etchevers et al., 2006; Jones et al., 2008; Keyte and Hutson, 2012; Passos-Bueno et al., 2009). The most common phenotypes related to inadequate NC formation and migration include cranio-facial defects, hearing loss, pigmentation and cardiac defects, as well as missing enteric ganglia. One

revealing example comes from the fact that 50% of Hirschsprung's patients, who have a partial or complete lack of the enteric PNS, have mutations in genes that are crucial for enteric NC cell migration along the gut (Mundt and Bates, 2010). Promising therapies using stem cells isolated from the gut have shown that an aganglionic colon can be colonised *de novo* to form a partial PNS (Sasselli et al., 2012). This emphasizes the need to understand the role of these genes during normal enteric NC migration to make such treatments not only reproducible but also tailored to a patient's needs.

### Perspectives

Historically, the field of NC cell migration was focused on cell guidance at the single-cell level, trying to understand how a given NC cell might use the local matrix and the available guidance signals to avoid a particular territory and to invade another. Recent findings, however, have rejuvenated the idea that NC cells actively interact with each other so as to cooperate while migrating. These new developments have established NC cells as a model for collective cell migration and have further highlighted the similarities between NC development and cancer metastasis, as well as wound healing and other developmental cell migration events such as gastrulation, lateral line migration or border cell migration. To take the field of NC cell migration even further, we need to better understand how multiple guidance cues are integrated to control migration at the population level, but also to look into how NC cells cooperate and interact with their surrounding tissues. To achieve this, classic experimental methods and genetics will need to be coupled with modern approaches, from quantitative biophysics and mathematical modelling to nanotechnologies.

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### Competing interests statement

The authors declare no competing financial interests.

### Development at a Glance

A high-resolution version of the poster is available for downloading in the online version of this article at <http://dev.biologists.org/content/140/11/2247.full>

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