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Review

Neural crest delamination and migration: From epithelium-to-mesenchyme transition to collective cell migration

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ABSTRACT

After induction and specification in the ectoderm, at the border of the neural plate, the neural crest (NC) population leaves its original territory through a delamination process. Soon afterwards, the NC cells migrate throughout the embryo and colonize a myriad of tissues and organs where they settle and differentiate. The delamination involves a partial or complete epithelium-to-mesenchyme transition (EMT) regulated by a complex network of transcription factors including several proto-oncogenes. Studying the relationship between these genes at the time of emigration, and their individual or collective impact on cell behavior, provides valuable information about their role in EMT in other contexts such as cancer metastasis. During migration, NC cells are exposed to large number of positive and negative regulators that control where they go by generating permissive and restricted areas and by modulating their motility and directionality. In addition, as most NC cells migrate collectively, cell–cell interactions play a crucial role in polarizing the cells and interpreting external cues. Cell cooperation eventually generates an overall polarity to the population, leading to directional collective cell migration. This review will summarize our current knowledge on delamination, EMT and migration of NC cells using key examples from chicken, *Xenopus*, zebrafish and mouse embryos. Given the similarities between neural crest migration and cancer invasion, these cells may represent a useful model for understanding the mechanisms of metastasis.

Introduction

The neural crest (NC) population is induced in the ectoderm at the interface between the neuroepithelium and the prospective epidermis at all levels of the antero-posterior axis, except for the most anterior neural ridge which becomes olfactory placode (Hall, 2008; Le Douarin and Kalcheim, 1999; Sauka-Spengler and Bronner-Fraser, 2008; Steventon et al., 2005). See also chapter by Bronner and Ledouarin (2012). The NC then separates from its neighboring neuroepithelial cells by a process called delamination that involves a partial or complete epithelium-to-mesenchyme transition (EMT) (Ahlstrom and Erickson, 2009; Alfandari et al., 2010; Berndt et al., 2008; Duband, 2010). Comparison between various animal models and different regions of the neural axis reveals that delamination occurs in a variety of developmental contexts and involves a range of cellular mechanisms. Despite apparent diversity, some general cell behaviors and common molecular effectors can be inferred, as summarized in the first part of this review. After separating from their surrounding tissues, NC cells migrate extensively throughout the embryo. They start their migration as a continuous wave, moving away from the neural tube, but quickly split into discrete streams (Gammill and Roffers-Agarwal, 2010; Hall, 2008; Kulesa et al., 2010; Kuo and Erickson, 2010; Kuriyama and Mayor, 2008; Le Douarin and Kalcheim, 1999; Theveneau and Mayor, 2011b). NC cells give rise to a plethora of derivatives including most of the neurons and all of the glial cells of the peripheral nervous system, pigment cells, a major part of the cartilage and bone of the craniofacial structures, endocrine cells, cardiac structures, smooth muscle cells and tendons (Dupin et al., 2006; Grenier et al., 2009; Hall, 2008; Kirby and Hutson, 2010; Le Douarin and Kalcheim, 1999; Le Douarin and Teillet, 1971; Minoux and Rijli, 2010; Theveneau and Mayor, 2011b). To arrive at their target region, NC cells must interpret multiple environmental signals that directly influence where they go and settle to differentiate. This suggests a model where external information is required for properly targeting subpopulations of NC cells to specific locations. The classical view that mesenchymal cells migrate as individuals with scarce contact between them has begun to change. Recent evidence has shown that they exhibit true collective cell migration as interactions between cells directly influence cell directionality and are essential for the interpretation of external cues (Carmona-Fontaine et al., 2008b; Clay and Halloran, 2010; Erickson and Olivier, 1983; Hörstadius, 1950; Khalil and Friedl, 2010; Klymkowsky et al., 2010; Kulesa and Fraser, 2000; Kulesa et al., 2010; Mayor and Carmona-Fontaine, 2010; Raible et al., 1992; Rorth, 2009; Teddy and Kulesa, 2004; Theveneau and Mayor, 2011b; Theveneau et al., 2010; Xu et al., 2006). Therefore, part of the overall directionality of NC cell migration is generated

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due to cooperative behaviors and cell–cell interactions. NC cell migration is a highly dynamic process in which NC cells adapt their behavior by permanently probing their local environment and interacting with other NC cells or neighboring cell types (Carmona-Fontaine et al., 2008b; Cerny et al., 2004; Hall, 2008; Kulesa and Fraser, 2000; Le Douarin and Kalcheim, 1999; Noden and Trainor, 2005; Parichy, 1996; Smith et al., 1997; Theveneau et al., 2010; Trainor et al., 2002). The second part of this review presents an overview of the early migratory routes, guidance molecules and role of cell–cell interactions, as well as a few relevant examples of homing to specific organs and arrest of migration. A detailed account of migration of neural crest to form the enteric nervous system is presented by Sasselli et al. (this volume). Finally, with EMT and collective cell migration in cancer progressively gaining clinical recognition (Friedl and Gilmour, 2009; Friedl and Wolf, 2003; Hanahan and Weinberg, 2011; Prall, 2007; Thiery et al., 2009; Wyckoff et al., 2007), NC cells have become an exciting model to study EMT and the interplay between cooperative behaviors and guidance molecules during invasive processes. Several interesting parallels between NC migration and cancer metastasis can be drawn and will be discussed at the end of this review.

Delamination: when the neural crest cells go their separate ways

The terms delamination and EMT are often used interchangeably in the NC field. Delamination defines the splitting of a tissue into separate populations regardless of the cellular mechanisms (Gilbert, 2010), in this case neural crest cells and their surrounding tissues. In contrast, EMT is a series of events at the molecular level orchestrating a change from an epithelial to a mesenchymal phenotype (Thiery et al., 2009). While it is true that all NC cells undergo EMT during their development, the timing and completion of EMT do not always match the timing of the delamination phase (Fig. 1). Therefore, it is important to use these terms carefully.

Dynamics of delamination and its variations along the antero-posterior axis

The presumptive NC population is located at the neural plate border (prospective dorsal neural tube) (Fig. 1A). In the cranial region, NC cells delaminate all at once (Figs. 1B–D). In mouse and *Xenopus* embryos this massive delamination occurs when the neural plate is still wide open (Figs. 1B–C; Hörstadius, 1950; Nichols, 1981, 1987; Sadaghiani and Thiebaud, 1987), while in birds it coincides with the fusion of the neural folds (Fig. 1D; Duband and Thiery, 1982; Le Douarin and Kalcheim, 1999; Theveneau et al., 2007). In all animal models, the trunk NC cells delaminate progressively, leaving the neuroepithelium one by one in a dripping fashion (Fig. 1E; Ahlstrom and Erickson, 2009; Berndt et al., 2008; Clay and Halloran, 2010; Davidson and Keller, 1999; Duband, 2010; Erickson and Weston, 1983; Kalcheim and Burstyn-Cohen, 2005). Delamination of the trunk NC cells starts after neural tube closure/formation but the time difference between the end of neurulation and NC departure can vary dramatically along the AP axis. In the chick embryo, for instance, rostral trunk NC cells delaminate a few hours after neural tube closure (Sela-Donenfeld and Kalcheim, 1999) while caudal-most NC cells emigrate one day after completion of neurulation (Osorio et al., 2009b). In the rostral trunk, the timing of NC delamination is tightly correlated with that of somitogenesis, with NC cells delaminating in front of early differentiating somites (Sela-Donenfeld and Kalcheim, 2000). However, cephalic regions are devoid of somites (Kos et al., 2001; Le Douarin and Kalcheim, 1999; Theveneau et al., 2007) and at caudal-most regions of the trunk, NC delamination is extremely delayed with respect to somite maturation (Osorio et al., 2009a, 2009b). Furthermore, neural tube closure and NC delamination are functionally uncoupled (Copp et al., 2003). In the homozygous *splotch* mutant (Pax3−/−) for instance, failure of neural tube closure does not lead to defects in delamination (Franz, 1992) and *splotch*/*curly tail* mice have an exaggerated spina bifida without exhibiting NC delamination defects (Estibeiro et al., 1993). All together, these observations suggest that, despite local influences from neighboring tissues, there is no common rule that links the timing and modes of NC delamination with neurulation or somitogenesis.

Molecular control of trunk neural crest cell delamination

In chick embryos, delamination is triggered by a BMP/canonical Wnt cascade involving Bmp4, Wnt1, Msx1 and c-Myb (Fig. 2A and Burstyn-Cohen et al., 2004; Karafiat et al., 2005; Liu et al., 2004; Sela-Donenfeld and Kalcheim, 1999). This cascade promotes EMT via activation of Snail2, Foxd3 and members of the SoxE family (Burstyn-Cohen et al., 2004; Cheung and Briscoe, 2003; Cheung et al., 2005; Sela-Donenfeld and Kalcheim, 2002). Snail2, Foxd3, Sox9 and Sox10 cooperate to orchestrate a Cadherin switch from N-Cadherin to Cadherin6B to Cadherin 7 and 11 (Chalpe et al., 2010; Cheung and Briscoe, 2003; Cheung et al., 2005; Dottori et al., 2001; McKeown et al., 2005; Nakagawa and Takeichi, 1995, 1998), activate β1-integrin (Cheung et al., 2005), modulate RhoB expression (Cheung and Briscoe, 2003; Liu and Jessell, 1998; McKeown et al., 2005), stimulate laminin synthesis and basal lamina degradation, promote cell survival, and maintain NC identity (Cheung et al., 2005; Dottori et al., 2001). Interestingly, a very similar gene regulatory network has been established for neural crest specification in all species (see review by Milet and Monsoro-Burq, this volume) suggesting that similar genetic cascades are used iteratively throughout NC development: for specification first and then for delamination. This is supported by the fact that data on NC specification show a high level of conservation across species (Aybar and Mayor, 2002; Nikitina and Bronner-Fraser, 2009; Nikitina et al., 2009; Steventon et al., 2005) and because the role of some factors can be distinguished temporally. For example, late inhibition of BMP signaling can block delamination without affecting Snail2 expression in the chick dorsal neural tube (Sela-Donenfeld and Kalcheim, 1999). This indicates that despite being first used for NC induction, Bmp signaling is then later reused for delamination purposes.

A BMP4/Wnt1 cascade is essential for the G1/S transition of NC precursors located in the dorsal part of the neural tube (Burstyn-Cohen and Kalcheim, 2002; Burstyn-Cohen et al., 2004). NC cells delaminate while in S-phase but show no synchronization prior to delamination. Inhibiting the G1/S transition in rostral trunk chick NC cells blocks delamination (Burstyn-Cohen and Kalcheim, 2002) and being in S-phase is therefore seen as a prerequisite for delamination to happen. However, all neuroepithelial cells, including non-delaminating populations located in mid- and ventral portions of the neural tube, properly cycle and exhibit interkinetic nuclear migration (Langman et al., 1966; Messier and Auclair, 1975). Cells undergoing mitosis have their nuclei near the apical side while cells in S-phase have their nuclei close to the basal side. Therefore, the entry in S-phase is, by itself, not sufficient to promote delamination. Moreover, premigratory NC cells located in the dorsal NT progress perfectly through the cell cycle before exiting the neural tube (Burstyn-Cohen and Kalcheim, 2002) and delamination can be blocked without affecting the cell cycle (Karafiat et al., 2005). This suggests that, despite being required for delamination in the rostral trunk of the chick embryo, G1/S transition is not a key event triggering the onset of migration.

Interestingly, the metalloproteinase ADAM-10 is expressed in the neural tube (Hall and Erickson, 2003) and both EMT and cell cycle regulation downstream of the BMP/Wnt cascade are linked through an ADAM10-dependent cleavage of N-Cadherin (Shoval et al., 2007). Briefly, ADAM10 cleaves the extracellular domain of N-Cadherin which helps to reduce cell–cell adhesion among NC cells and loosen the bond between NC cells and neuroepithelial cells. The remaining

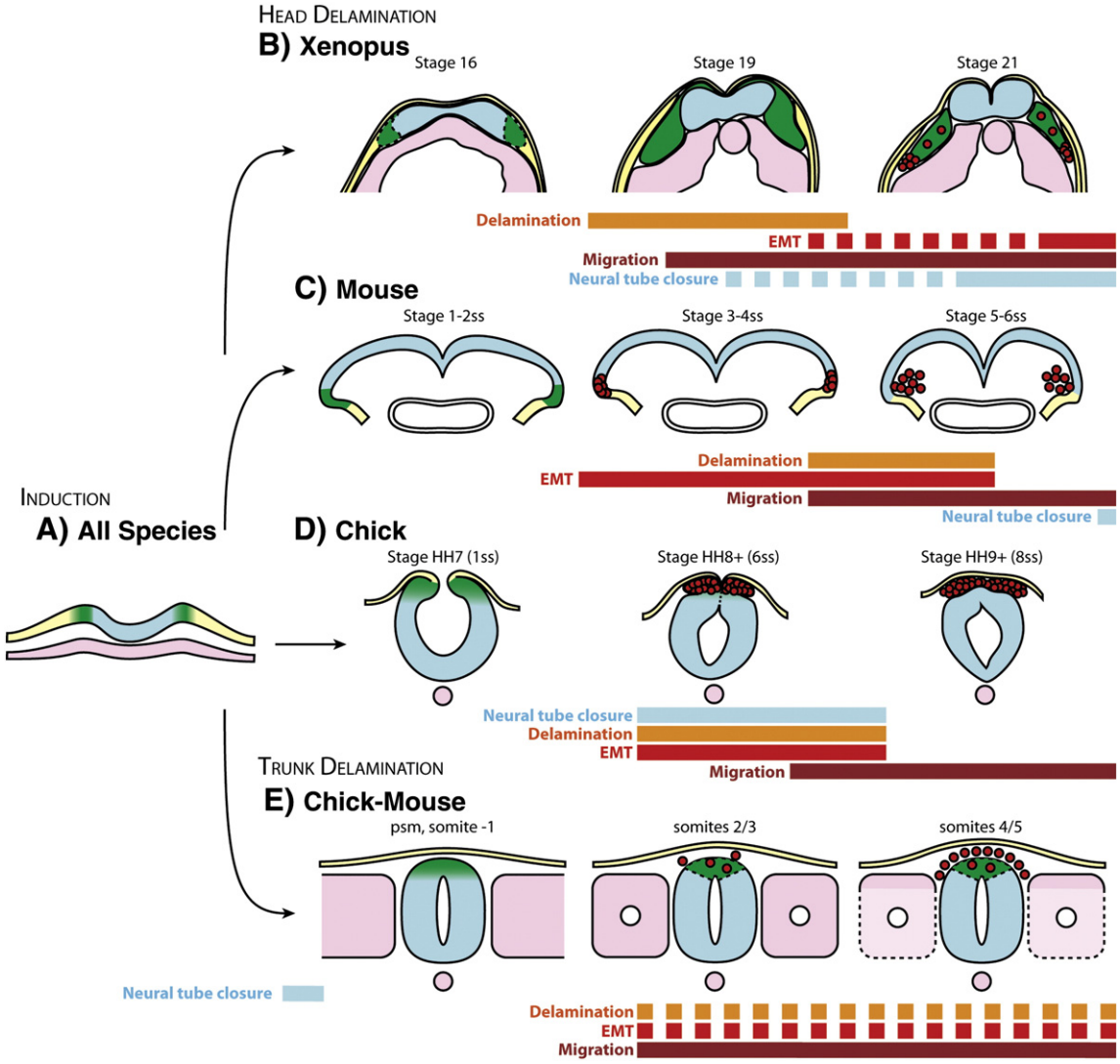

Fig. 1. Delamination of the cephalic and trunk neural crest cells. (A) Basic organization of the dorsal region of a vertebrate embryo at early neurula stage. NC cells (green) are induced at the border of the open neural plate (blue). (B) *Xenopus* cephalic NC cells separate from the open neural plate and the sensory layer of the ectoderm between stages 16 and 18 and start migrating as a cohesive group (stage 19). While migration proceeds, NC cells become progressively more mesenchymal (red cells). Based on Slug and Foxd3 expressions on histological sections and electron microscopy after Schroeder (1970). (C) Delamination of mouse cephalic NC cells starts at open neural plate stage. NC cells undergo an EMT, delaminate and start migrating within a few hours. Modified after Nichols (1987). (D) Delamination of chick cephalic NC cells involves a massive EMT. All cells delaminate at once and start migrating soon after. Based on the dynamic of Ets1 expression in the mesencephalon. Modified after Theveneau et al. (2007) (E) Delamination of chick/mouse rostral trunk NC cells. Premigratory NC cells that are located in the dorsal part of the closed neural tube face the presomitic mesoderm (psm). Delamination starts in front of the second/third newly formed somites. NC cells undergo EMT one by one, delaminate in a dripping fashion and start migrating as soon as they leave the neural tube. Modified after Kos et al. (2001) and Sela-Donenfeld and Kalcheim (1999). Note that neural tube closure and NC delamination are not synchronized across species. Also note that the timing of delamination and EMT do not necessarily coincide. Premigratory NC territory and NC cells are shown in green, red round cells represent mesenchymal NC cells or NC cells undergoing EMT. The neural plate/tube is in blue, non-neural ectoderm and the sensory layer of the ectoderm are in yellow, mesoderm and its derivatives are in pink.

domain of N-cadherin is further cleaved into a cytoplasmic fragment (CTF2) activating cyclin-D1 expression. Cyclin-D1 is required for cell cycle progression but does not systematically promote G1/S transition in the neural tube (Lobjois et al., 2004; Megason and McMahon, 2002). The activation of the BMP/Wnt cascade is linked to somite maturation, as early differentiating somites are thought to release a still unidentified factor that blocks Noggin expression in the dorsal neural tube (Sela-Donenfeld and Kalcheim, 2000). This in turn unleashes the BMP/Wnt cascade. Alternatively, presomitic mesoderm and newly formed somites could be the source of a factor maintaining Noggin expression in the dorsal neural tube that could be lost upon somite differentiation. Furthermore, at the time of delamination, dorsal neural tube cells express Cv2 (homologue of crossveinless-2) which promotes BMP signaling possibly by acting as a carrier for BMP4 (Coles et al., 2004; Conley et al., 2000). Inhibition of Noggin or Cv2 overexpression both lead to early departure of NC cells while maintenance of Noggin blocks NC delamination (Coles et al., 2004; Osorio et al., 2009a; Sela-Donenfeld and Kalcheim, 1999). The factors regulating the timing and distribution of Cv2 expression at the time of NC cell emigration are unknown, but some work done in Drosophila indicates that Cv2 is a target of Bmp signaling, suggesting a putative feedback loop (Serpe et al., 2008). Finally, the secreted molecule Noelin-1 is progressively restricted to the neural fold and its overexpression leads to an excess of NC cells, possibly through an upregulation of Snail2 (Barembaum et al., 2000). However, its early expression, before that of Snail2, suggests that its overexpression expands the NC territory rather than specifically triggering the delamination. It should be noted that the role of most of these proteins, such as ADAM10, Noggin, Cv-2

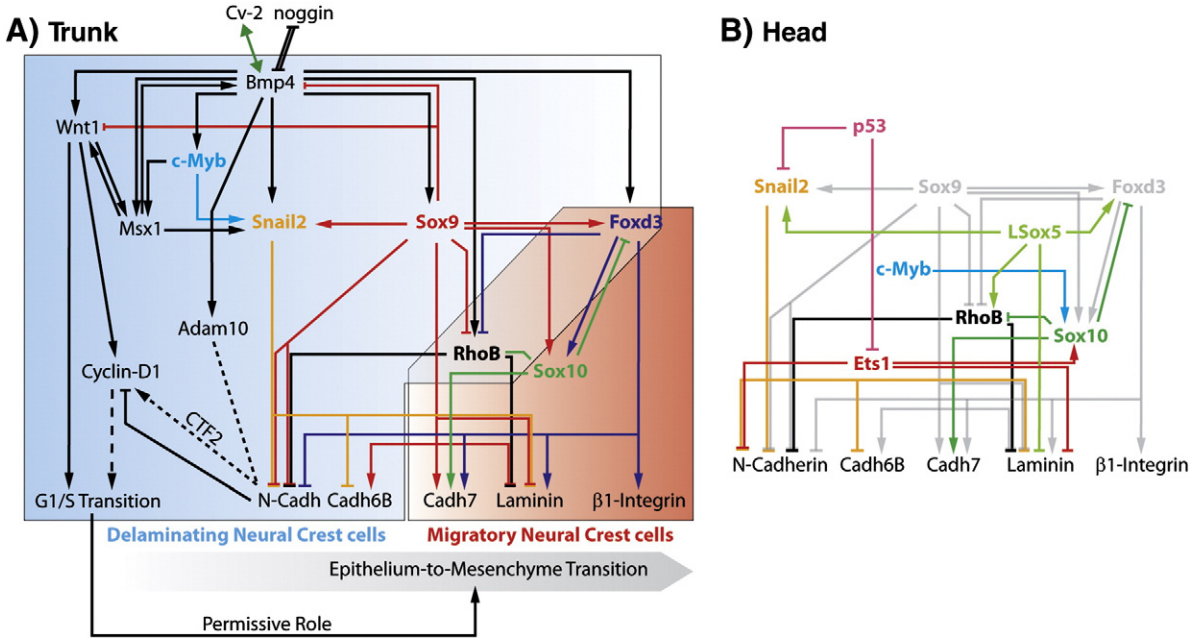

Fig. 2. Molecular cascade controlling NC cell delamination at rostral trunk and cephalic levels in chick embryo. (A) Molecular control of rostral trunk delamination. Premigratory NC crest cells express Bmp4 and the Bmp inhibitor Noggin. Noggin expression is progressively lost while Cv2, a Bmp carrier/enhancer, expression goes up. This change unleashes Bmp4 signaling, which triggers a Wnt1-dependent cascade. The Bmp4–Wnt1 axis activates a set of transcription factors (including but not restricted to Snail2, Sox9 and Foxd3) that control the EMT by modifying cell–cell and cell–matrix adhesion molecules. In parallel, Wnt1 promotes cell cycle progression through Cyclin-D1 (left part of the panel). Finally, the metalloprotease ADAM10 is activated downstream of Bmp4 and degrades N-Cadherin. Cleavage of N-Cadherin contributes to the loss of cell–cell adhesion and promotes cell cycle progression through Cyclin-D1 activation. See text for details. (B) Molecular control of cephalic delamination. The tumour suppressor p53 is expressed in the dorsal neural tube before delamination and inhibits Snail2 and Ets1 expression. p53 disappearance allows Snail2 and Ets1 expression levels to go up and triggers the delamination. Alongside Snail2 and Ets1 the cascade involves several transcription factors such as LSox5, Sox9 and Foxd3, but the relationship between these factors at cephalic levels is poorly understood. Putative roles for Sox9 and Foxd3 are based on their known functions at trunk levels. Networks at both trunk and cephalic levels are based on gain- and loss-of-function experiments performed in vivo in the chick embryo, see main text for references. Arrows and lines are color-coded in register with the genes they originate from. Single lines/arrows mean that one gene is sufficient to activate/inhibit a specific downstream effector. Double lines/arrows mean that a co-expression is required to activate/inhibit a specific downstream effector. For example, Snail2 alone can inhibit Cadherin-6B expression but Snail2 and Ets1 co-expression is required to block N-Cadherin expression. See main text for references.

and Noelin-1, on NC delamination has been mainly studied in chick, with no equivalent analysis in other species.

Altogether, these data indicate that the NC delamination in the chick rostral trunk is the consequence of an EMT orchestrated by Snail2, Foxd3 and SoxE factors, which act downstream of BMP4/Wnt1 and whose timing is locally bound to somitogenesis.

Molecular control of NC delamination along the AP axis: how to make ends meet?

The head is devoid of somites and therefore cephalic NC cells do not face somitic mesoderm, with the exception of the NC cells exiting from the caudal hindbrain at post-otic levels. In addition, migratory cephalic NC cells express several BMP and Wnt inhibitors (Graham et al., 1994; Tzahor et al., 2003) making it unlikely that they require Bmp signaling to start their migration. Moreover, overexpression of Noggin and dominant negative BMP receptors are unable to block cephalic NC delamination (Kalcheim and Burstyn-Cohen, 2005; Kirby and Hutson, 2010). Furthermore, cranial NC cells' departure is not linked to the G1/S transition of the cell cycle (Theveneau et al., 2007). In the posterior trunk, caudal-most NC is not synchronized with somitogenesis (Osorio et al., 2009b). Prospective caudal-most NC cells in the dorsal neural tube fail to downregulate Noggin expression in response to somite differentiation (Osorio et al., 2009a) and consequently start delaminating with a 24-hour delay. In this region, the delamination of these late emigrating NC cells is under the control of a Wnt3a-dependent, but BMP4/Wnt1-independent, signaling pathway. All these observations suggest that upstream regulators of the cephalic NC cells and caudal-most NC cells delamination are different than upstream regulators identified so far in the rostral trunk.

Flexible recipe for the delamination cocktail

At the transcriptional level, comparison between head and trunk NC cells highlight some differences. In the head, additional factors such as Ets1, Id2 or LSox5 may account for the all-at-once mode of delamination of cephalic NC cells (Fig. 2B and Martinsen and Bronner-Fraser, 1998; Perez-Alcala et al., 2004; Tahtakran and Selleck, 2003; Theveneau et al., 2007). However, Id2 is expressed early and when ectopically expressed is able to convert non-NC cells into NC while LSox5 and Ets1 are not able to ectopically induce NC cell identity. Therefore, Id2 seems more related to fate decision at the neural border rather than being involved in specifically triggering delamination. Targeted overexpression of Id2 after NC specification but prior to delamination is required to address its putative role in delamination. Interestingly, the tumour suppressor p53 (Green and Kroemer, 2009; Kastan, 2007) is expressed in the neural folds prior to cephalic NC cells delamination and its disappearance matches the onset of NC emigration. Stabilization of p53 strongly inhibits Snail2 and Ets1 expression and dramatically reduces the number of NC cells delaminating (Rinon et al., 2011). This suggests that reduction of p53 levels might lead to a peak of Snail2 and Ets1 in the dorsal part of the neural tube promoting delamination (Fig. 2B). However, Ets1 binds to p53 promoter and can activate its expression (Venanzoni et al., 1996). Therefore, it is possible that a negative feedback loop is taking place between Ets1 and p53 that would restrict the period of delamination to that of the peak of Ets1 expression. In support of a joint action of Snail2 and Ets1, co-electroporation of these factors is indeed sufficient to promote the delamination of NC cells from ectopic portions of the neural tube all along the AP axis (Theveneau et al., 2007). In addition, ectopic expression of Ets1 in the NC territory at trunk levels is sufficient to convert the slow-paced, S-phase-bound trunk delamination into a massive

cranial-like delamination independent from the cell cycle progression (Theveneau et al., 2007). Finally, Ets1, alongside Sox9 and c-Myb, has been proposed as a regulator of Sox10 expression (Betancur et al., 2010) and the data described above suggest that Ets1 could be a key factor explaining the massive emigration of NC cells at cephalic levels. However, Ets1-knockout mice do not seem to have cranial NC crest defects (Bartel et al., 2000), which suggests some degree of redundancy in mice, a common feature for many neural crest transcription factors.

Other interesting variations can be observed along the AP axis. Despite lacking Foxd3 expression and having only a transient Sox10 expression in chick (Cheng et al., 2000; Dottori et al., 2001; Kos et al., 2001), rhombomere 3 produces proper migratory NC cells (Couly et al., 1998; Lumsden et al., 1991). In rostral trunk, Snail2 and Foxd3 expressions in the dorsal neural tube are lost several hours before the end of NC cells emigration but they are maintained during delamination and migration in cephalic NC cells (del Barrio and Nieto, 2002; Kos et al., 2001; Nieto et al., 1994). In addition, Snail2 ectopic expression is unable to disorganize the neural tube or promote ectopic NC delamination (Cheung et al., 2005; del Barrio and Nieto, 2002; Dottori et al., 2001; Theveneau et al., 2007) and Snail1/Snail2 double knockout mouse shows no sign of delamination defects (Murray and Gridley, 2006). On the other hand, Foxd3 can downregulate N-cadherin and promote β1-integrin activation and Cadherin-7 expression but leads to very few ectopic delaminating cells (Cheung et al., 2005; Dottori et al., 2001; Kos et al., 2001).

Taken together, these data suggest that a combination of factors is required to promote delamination of neuroepithelial cells with the ability to form neural crest, but they also indicate that the precise mixture varies from region to region and over time in a given region.

Downstream targets of the delamination cocktail

The downstream targets of the mixture transcription factors responsible for regulating delamination are also likely to vary. However, modulation of cadherin activity/expression at the time of NC emigration is a common thread between NC cell populations at different axial levels and across species. NC cells usually switch from a strong, classical cadherin-based cell–cell adhesion (N-Cadherin) to a weaker type of cell–cell adhesion based on type II-cadherins (Cadherin-6/6B/7/11, Figs. 2A–B; Chalpe et al., 2010; Inoue et al., 1997; Nakagawa and Takeichi, 1995, 1998; Simonneau et al., 1995; Vallin et al., 1998). In chick, the successive changes of Cadherin expression have been proposed as a key process not only to promote delamination but also to define the pre-migratory NC territory in the dorsal part of the neural tube. Non-NC cells in the neural tube strongly express N-cadherin while premigratory NC cells have only a weak N-Cadherin expression and a strong Cadherin-6B expression (Akitaya and Bronner-Fraser, 1992; Duband et al., 1988; Nakagawa and Takeichi, 1995). This differential expression is believed to prevent mixing between NC and non-NC cells. The subsequent loss of Cadherin-6B under the control of Snail2 (Coles et al., 2007; Taneyhill et al., 2007) and the activation of Cadherin-7 by Foxd3/Sox10 (Cheung et al., 2005) and Cadherin-11 in a Wnt-dependent manner (Chalpe et al., 2010) would then promote the delamination by a similar cell sorting-like mechanism pushing Cadherin6B−/Cadherin7/11+ NC cells out of the dorsal neural tube.

However, complete inhibition of N-Cadherin expression does not seem to be an absolute pre-requisite for delamination since migratory cephalic NC cells in Zebrafish, *Xenopus* and chick show various levels of N-Cadherin expression (Piloto and Schilling, 2010; Theveneau et al., 2007, 2010). Moreover, *Xenopus* NC cells do not lose their cell–cell adhesion at the time of delamination. They separate from the folding neural plate and the sensory layer of the ectoderm as a tight group, remain as such until the beginning of migration when they exhibit a more loose and mesenchymal organization (Alfandari et al., 2010; Sadaghiani and Thiebaud, 1987; Theveneau et al., 2010). This suggests that, at least in *Xenopus*, the delamination of cephalic NC cells involves a local loss of cell–cell adhesion between the NC cells and their neighboring tissues but no global shift of cell–cell adhesion properties among NC cells. Whether a similar local regulation of cell–cell adhesion happens in species other than *Xenopus* remains to be investigated.

Apart from expression levels, cadherin activity in NC cells can also be regulated by cleavage but the direct link with delamination is unclear. ADAM10 expression has been reported in trunk NC cells in mouse (Reiss et al., 2005), suggesting that a mechanism similar to the one described above for chick NC cells could also be at work in mouse NC cells though this remains to be assessed. Cranial *Xenopus* NC cells express ADAM13 (Alfandari et al., 1997, 2001). However, the ADAM13-dependent degradation of Cadherin-11 is required for migration but not delamination (McCusker et al., 2009). Finally, cranial NC cells in chick, mouse and *Xenopus* express other metalloproteinases bearing Cadherin-cleaving capabilities and their regulators (Brauer and Cai, 2002; Cai and Brauer, 2002; Cai et al., 2000; Cantemir et al., 2004; Duong and Erickson, 2004; Giambernardi et al., 2001). This suggests that cadherin shedding may be a general process during NC development although its precise relationship with delamination is poorly understood. An interesting example comes from MMP2 inhibition that specifically blocks cephalic NC delamination in chick but does not prevent migration of already delaminated NC cells (Duong and Erickson, 2004). Interestingly, downregulation of Cadherin activity may be linked to the acquisition of migratory abilities through a crosstalk between cadherins and integrins (Monier-Gavelle and Duband, 1997) suggesting that the loss of cell–cell adhesion could directly promote cell motility on a short-time scale. Such direct cross-talk could act to refine actions of upstream regulators like Foxd3 that can modulate both cell–cell adhesion and integrin activity (Cheung et al., 2005).

In summary, the switch from a strong cell adhesion required to maintain epithelial integrity to a weak cell–cell adhesion promoting separation from the epithelium and allowing cell migration may be a general step during NC development, but it is likely to be achieved using a range of strategies (change in expression levels, cadherin switch, shedding) and resulting in different outcomes (separation from the surrounding tissues, separation from other NC cells, onset of migration).

A range of cellular strategies to exit the neural tube

Despite much information about the different events taking place at the time of delamination, little was known about the real sequence of these events at the time of emigration until improvements in in vivo time-lapse microscopy allowed for the visualization of NC cells separating from the neural tube. Elegant studies in chick trunk and zebrafish hindbrain (Ahlstrom and Erickson, 2009; Berndt et al., 2008) showed that most cells followed the expected pattern of events involved in EMT. A majority of cells was seen losing their cell–cell adhesion and apico-basal polarity first. However, many exceptions were observed suggesting that there is no strict pattern. For instance, cells can start their emigration from the neural tube without downregulation of the cell–cell adhesion complex, leaving cellular pieces behind. In addition, the loss of apico-basal polarity can occur before or after the translocation of the cell body towards the basal side. Importantly, these works also indicate that loss of cell–cell adhesion is not an absolute prerequisite for the acquisition of migratory capabilities. Protrusive activity observed during delamination shows that NC cells form blebs and lamellipodia (Ahlstrom and Erickson, 2009; Berndt et al., 2008) as previously suggested by electron microscopy in mouse neural tube (Erickson and Weston, 1983). Altogether these in vivo observations demonstrate that there is no strict ordered plan at the NC cell population level to perform the delamination.

Instead, it seems that NC cells engage in a variety of cell behaviors which could maximize the chances of success. This is consistent with the complex transcriptional regulatory network activated in the neural crest, with different modules controlling distinct cell behaviors in parallel and not in a sequential fashion (Figs. 2A–B).

Neural crest cell migration

Where do they go?

The cephalic NC cells start migrating as a continuous wave of cells, moving away from the neuroepithelium, and quickly splitting into distinct streams (Figs. 3A–B; Hall, 2008; Hörstadius, 1950; Kulesa et al., 2010; Le Douarin and Kalcheim, 1999; Theveneau and Mayor, 2011b). This pattern of migration shows little variation between species. The cephalic NC cells contributing to cranial ganglia will stop in a relatively dorsal position while the subpopulations forming cartilages and bones of the face and neck will continue further ventrally and invade the branchial arches. At post-otic levels some NC cell populations migrate even further. The cardiac NC cells, arising posterior to the otic placode from the anterior limit of rhombomere 4 and caudalward, migrate to the developing heart (Kirby and Hutson, 2010), and the enteric crest arising from somites 1 to 7 colonize the gut (see review by Vasselli et al., this volume).

In the trunk however, the timing and the trajectories of NC cells show apparent differences between species (Figs. 4A–E; Collazo et al., 1993; Hall, 2008; Kelsh et al., 2009; Kuo and Erickson, 2010; Kuriyama and Mayor, 2008; Le Douarin and Kalcheim, 1999; Raible et al., 1992). In chick and mouse embryos, NC cells start migrating ventrally in a non-segmented fashion between the neural tube and the early formed somites, favoring the intersomitic space. Following somite maturation, NC cells pass through the anterior half of the sclerotome and along the basement membrane of the dermomyotome (Figs. 4A–B, E; Erickson and Weston, 1983; Hall, 2008; Kuriyama and Mayor, 2008; Le Douarin and Kalcheim, 1999; Thiery et al., 1982a). These trunk NC cells of the ventral pathway will form the sympathetic ganglia, the dorsal root ganglia, glial cells along the dorsal and ventral roots of the spinal cord and the boundary cap cells (Le Douarin and Kalcheim, 1999; Vermeren et al., 2003). Another wave of NC cells undertakes a dorsolateral migration in between the dorsal ectoderm and the dermomyotome to later differentiate as melanocytes. In mouse, both routes are invaded simultaneously, while in chick the second wave invades the dorsolateral path with a 24-hour delay (Figs. 4A–B; Erickson and Goins, 1995; Kelsh et al., 2009; Kuo and Erickson, 2010). In zebrafish, trunk NC cells start migrating along a medial pathway in between the somites and the neural tube (Figs. 4C, E). NC cells are aligned with slow muscle cells located in the middle part of the somite (Honjo and Eisen, 2005; Raible et al., 1992). 4 h after the onset of migration along the medial pathway, NC cells commence migrating on a lateral pathway between the epidermis and the somite (Fig. 4C; Raible et al., 1992). In *Xenopus*, trunk NC cells mostly pass in between the neural tube and the somite at the level of the caudal somite (Figs. 4D–E; Collazo et al., 1993), whereas few NC cells migrate in the lateral pathway under the dorsal ectoderm. Interestingly, in chick and mouse the dorsolateral route is only used by NC cells restricted to the melanoblastic lineage but in zebrafish and *Xenopus* pigment cells precursors use both ventral and dorsolateral routes (Collazo et al., 1993; Kelsh et al., 2009). Some of the differences observed between all species are likely related to the fact that the sclerotome in fish and frogs is extremely reduced compared to chick and mouse, and plays no role in restricting NC cell migration. Additionally, in fish and frogs some trunk NC cells migrate straight up where they contribute mesenchymal and pigment cells to the dorsal fin (Collazo et al., 1993; Hall, 2008; Jesuthasan, 1996; Sadaghiani and Thiebaud, 1987; Thisse et al., 1995).

It has been proposed that antero-posterior patterning of the neural tube controls the exit point of the different subpopulations of NC cells. These NC groups would express markers in register with their region of emigration and invade regions of similar identities. To some extent, patterns of Hox and ephrins/Eph gene expression support such model (Adams et al., 2001; Couly et al., 1998; Creuzet et al., 2002, 2005; Davy et al., 2004; Kuriyama and Mayor, 2008; Mellott and Burke, 2008; Pasqualetti et al., 2000; Rijli et al., 1993, 1998; Ruhin et al., 2003; Smith et al., 1997; Trainor and Krumlauf, 2001; Trainor et al., 2002). However, if some pre-patterning exists, the NC cell population is mainly plastic and adapts to the local context. The more widely accepted idea is now that NC cells integrate the external signals present in the environment, be it guidance cues or contacts with other NC cells, and choose a path accordingly. The signals regulating NC cell migration at cephalic and trunk levels are discussed below.

Molecular control of cephalic neural crest cell migration

Negative regulators of cephalic neural crest cell migration

Cephalic NC cell migration is controlled by a complex set of negative and positive external regulators. The splitting of the NC continuum into separate subpopulations has been mainly attributed to two class of signaling molecules: ephrins and their Eph receptors and class3-semaphorins and their neuropilin/plexin receptors (Figs. 5A–B) which prevent entry into specific zones by inducing the collapse of cell protrusions. Cephalic NC cells in mouse, chick and *Xenopus* express different combinations of ephrins and Eph receptors (Adams et al., 2001; Baker and Antin, 2003; Davy et al., 2004; Helbling et al., 1998; Mellott and Burke, 2008; Smith et al., 1997). This ephrin/Eph code can be in register with the ephrin/Eph code expressed by the mesoderm present in the region invaded by NC cells as in *Xenopus* (Smith et al., 1997) or NC cells and their surrounding tissues can express complementary patterns of ephrins and Eph as in chick (Fig. 5A and Baker and Antin, 2003; Mellott and Burke, 2008). Inhibition of ephrin/Eph signaling leads to ectopic migration outside the migratory routes indicating that they contribute to the maintenance of NC-free regions. In addition, impairing ephrin/Eph can lead to some degree of cell mixing among the NC streams. More precisely, NC cells that would normally be part of a given stream would integrate another one (Smith et al., 1997). These results suggest that ephrin signaling is required to create the NC-free regions but also is involved in a cell sorting process that targets specific subpopulations of NC cells to a specific migratory stream. This is most certainly achieved by preventing NC cells having different ephrin/Eph profile to share the same migratory stream and by forbidding entry into areas where the surrounding tissues exhibit another ephrin/Eph code.

Cephalic NC cells also express neuropilins 1 and 2 (Nrp1/2) (Fig. 5B; Eickholt et al., 1999; Gammill et al., 2007; Koestner et al., 2008; Osborne et al., 2005; Schwarz et al., 2008; Yu and Moens, 2005). These two neuropilins associate with members of the plexinA family to form a receptor specific for the secreted members of the class3-semaphorins in which neuropilins are required for the binding to class3-semaphorins and plexin for intracellular signaling (Eickholt, 2008; Jackson and Eickholt, 2009; Kruger et al., 2005). Studies in chick, zebrafish and mouse have directly involved several members of the class3-semaphorin family in the formation of discrete streams of NC cells (Eickholt et al., 1999; Gammill et al., 2007; Osborne et al., 2005; Schwarz et al., 2008; Yu and Moens, 2005). When semaphorin signaling is impaired, NC cells invade NC-free zones that are normally present in between the streams. The consequences of the absence/inhibition of one of the neuropilins or the semaphorins are not dramatic. However, when several semaphorin are targeted or when the signaling is massively disturbed by addition of soluble neuropilin, reducing the amount of available semaphorins in the milieu, the NC-free zones are abolished. However, their role at later stages of cephalic NC migration is unclear since NC cells invade the branchial

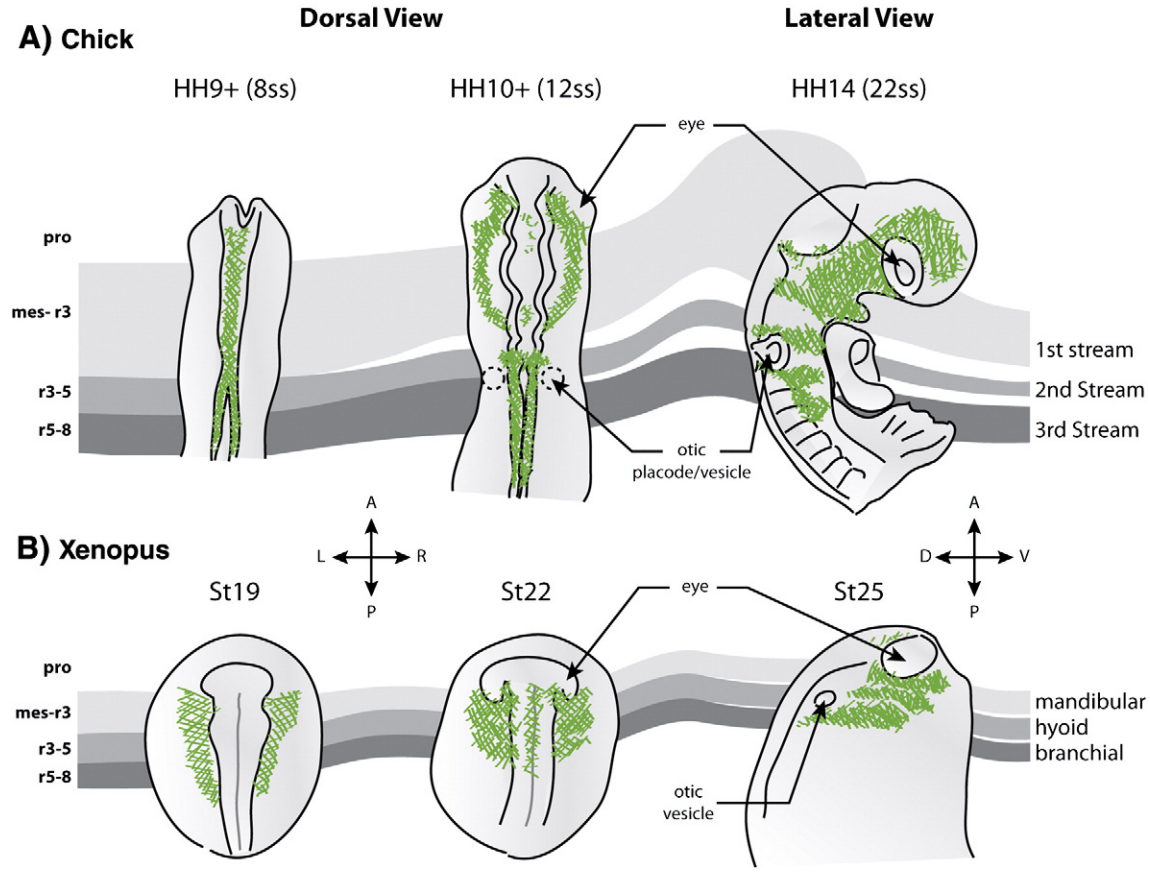

Fig. 3. Early migration of cephalic NC cells. (A) Migration of chick cephalic NC cells starts at mesencephalic levels around stage HH9+ and progresses anteriorly and posteriorly. NC cells migrate around the eyes and towards the ventral portions of the face. By stage HH10+ migration starts at mid- and posterior hindbrain levels (from r4 caudalward). At stage HH14, three streams of NC cells, separated by two NC-free regions located in front of r3 and r5, are clearly visible. The most ventral NC cells invade the branchial arches and the third stream progressively splits in two. Based on the dynamics of Snail2, Foxd3 and AP2 expressions and HNK1 staining at these stages. (B) Migration of *Xenopus* cephalic NC cells starts around stage 19 all across the cephalic region but NC cells forming the mandibular stream are slightly ahead of the more posterior streams. By stage 22, three bulges, located next to the neuroepithelium and reminiscent of the streams, are visible but no clear NC-free regions are formed yet. At stage 25, NC cells are now divided in three streams called mandibular (m), hyoid (h) and branchial (b) streams, separated by NC-free regions. The third stream will later split into two and eventually three streams (not shown). Based on the dynamics of Snail2 and Twist expression at these stages. Homologous streams in chick and *Xenopus* are coded in similar shades of gray for comparison. Note the compressed hindbrain area of *Xenopus* compared to chick and the expanded mesencephalon in chick compared to *Xenopus*. HH, Hamburger–Hamilton stages of chick embryo development; mes, mesencephalon; pro, proencephalon; r, rhombomere; ss, somites.Nieuwkoop and Faber stages of *Xenopus* embryos.

arches in which class3-semaphorins are expressed (Gammill et al., 2007). This observation suggests that NC cells may progressively lose the ability to respond to class3-semaphorins. This possibility is supported by the fact Nrp-1 is involved in VEGF signaling at later stages when NC cells enter the second branchial arch (McLennan and Kulesa, 2010; McLennan et al., 2010), suggesting that Nrp1 may first be associated with plexins to relay semaphorin signaling and then cluster with VEGFR to mediate VEGF signaling. Alternatively, semaphorin signaling could switch from inhibiting to promoting migration. Such a change has been previously described in axonal guidance (Castellani et al., 2000; Falk et al., 2005). Interestingly, post-otic NC cells that invade the cardiac region respond positively to Semaphorin-3 C (Toyofuku et al., 2008), further supporting a dual role for semaphorin signaling in patterning NC cell migration where class3-semaphorin would first split the NC population and then attract subpopulations to specific locations.

Alongside Ephrin and Semaphorin, the EGF-like receptor ErbB4 is expressed in rhombomere 3 while one of its ligands, neuregulin 1, is expressed in r2 and r4 (Golding et al., 2000, 2004). In mice lacking ErbB4, some NC cells from r4 migrate into the mesenchyme adjacent to r3 suggesting that ErbB4 signaling is essential for the production of an inhibitory cue produced by this rhombomere and released in the mesenchyme opposite. The downstream targets of ErbB4 signaling in this context remain unknown but ErbB4 does need a rhombomere 3-specific context to maintain the NC-free region adjacent to its expression domain since a rhombomere 5 expressing ErbB4 cannot maintain the NC-free region when grafted into r3 position (Golding et al., 2004).

Besides inhibitory cues, a massive apoptosis, restricted to the dorsal neural tube of the rhombomeres 3 and 5 in chick (Graham et al., 1993) led to the idea that the formation of the cephalic streams may be due to a specific elimination of NC cells from odd-numbered rhombomeres by programmed cell death. However, analysis by grafts and dye injections clearly showed that, in chick, all rhombomeres do produce NC cells (Couly et al., 1998; Lumsden et al., 1991) including r3 and r5 whose cells quickly join adjacent streams (Birgbauer et al., 1995; Kulesa and Fraser, 1998; Sechrist et al., 1993). In addition, chick and mouse rhombomeres 3 and 5 produce a large amount of NC cells when transplanted in r2 or r4 positions (Ellies et al., 2002; Graham et al., 1994; Kulesa et al., 2004). Moreover, blocking apoptosis has no effect on the formation of the streams (Ellies et al., 2002). Finally, although NC apoptosis has been linked to cell specification in *Xenopus* (Tribulo et al., 2004), no specific pattern of apoptosis has been found in the hindbrain of frogs (including *Xenopus*), zebrafish and mouse embryos at the time of NC cell emigration (Del Pino and Medina, 1998; Ellies et al., 1997; Hensey and Gautier, 1998; Kulesa et al., 2004). Consequently, targeted apoptosis is unlikely to play an active role in the formation of the NC-free zones.

Cephalic NC cells also encounter physical barriers that shape the migratory streams. The otic placode/vesicle is the main obstacle of the early migrating cephalic NC cells. Interestingly, the otic placode

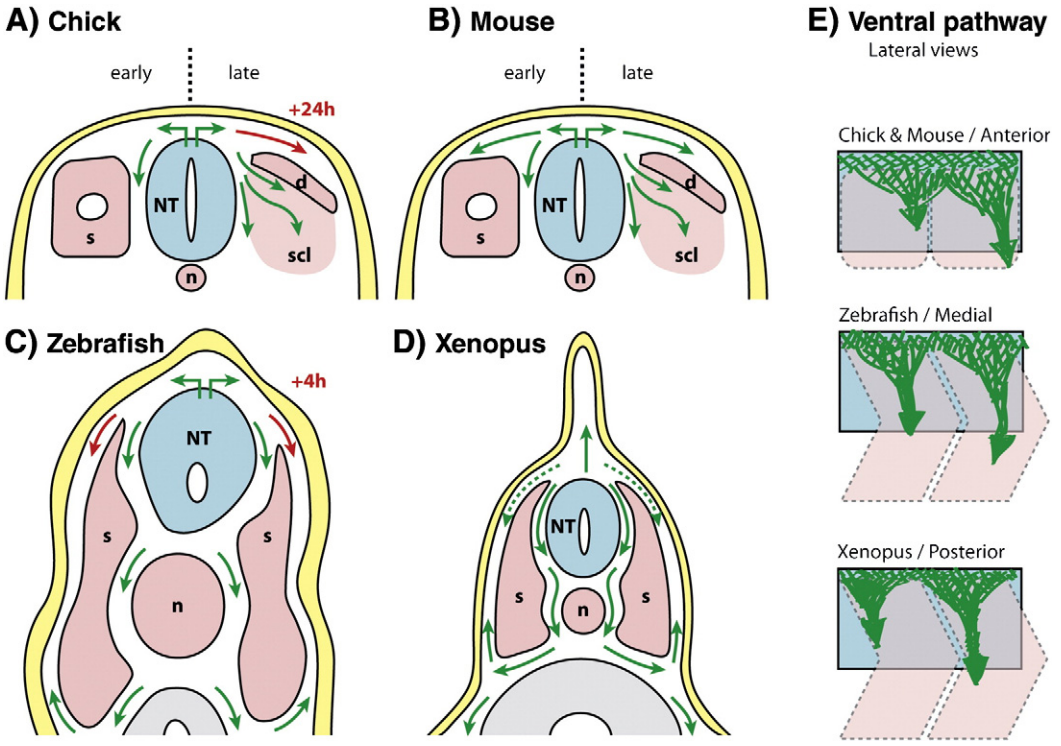

Fig. 4. Early migration of trunk NC cells. (A) Migration of chick trunk NC cells first starts between the neural tube and the epithelial somite and proceeds through the sclerotome upon somite differentiation. NC cells eventually invade the space underneath the dorsal ectoderm approximately 24 h after the onset of migration at one given level. After Le Douarin and Kalcheim (1999) and references therein. (B) Mouse trunk NC cells migration follows a dynamic similar to chick trunk NC cells however all pathways of migration are invaded simultaneously. No delay is observed for the migration under the ectoderm. In both chick and mouse only melanocyte precursors are able to use the dorso-lateral pathway under the ectoderm. (C) Migrating zebrafish trunk NC cells use two main routes: one in between the somites and the neural tube, another underneath the ectoderm. The different lineages of pigment cells show different preferences for the two routes. Iridophores use the ventral path and xantophores use the dorsolateral path, while melanophores use both routes. Pigment cells using the ventral pathway will eventually pass around the somites and migrate tangentially towards the skin. Migration on the dorsolateral path starts after a 4-hour delay. Modified after Raible et al. (1992) and Kelsh et al. (2009). (D) Migration of *Xenopus* trunk NC cells uses two pathways similar to zebrafish trunk NC cells. However, only very few cells use the dorso-lateral path. Melanocytes precursors using the ventral route will migrate around the somites to reach the skin. Modified after Collazo et al. (1993). (E) Lateral view of trunk NC cell migration in chick, mouse, zebrafish and *Xenopus* embryos. Chick and mouse NC cells pass through the anterior sclerotome whereas zebrafish NC cells pass in between the neural tube and the somites at the mid-somitic level. Finally, *Xenopus* NC cells migrate in between the neural tube and the somites but are aligned with the posterior half of the somites. Color-code used to label tissues is similar to Fig. 1. d, dermomyotome; n, notochord; NT, neural tube; s, somite; scl, sclerotome.

is directly adjacent to the rhombencephalon in chick and mouse while in fish and frogs it is positioned at a distance (Kulesa et al., 2004; Sadaghiani and Thiebaud, 1987; Schilling and Kimmel, 1994; Sechrist et al., 1993; Smith et al., 1997). This direct apposition forces chick and mouse NC cells facing the otic placode to migrate rostrally and caudally soon after their delamination. However, in zebrafish and *Xenopus* embryos NC cells from the otic level can start migrating as a continuous wave in the mesenchyme directly adjacent. The otic vesicle expresses members of the class3-semaphorin family (Bao and Jin, 2006; Eickholt et al., 1999) but it is not clear if NC cells actually respond to these local inhibitory cues since grafts of ectopic otic vesicles attract, rather than repel, NC cells (Sechrist et al., 1994). The physical obstacle created by the otic is therefore the most likely explanation for the change of direction of NC cells in its vicinity.

Positive regulators of cephalic neural crest cell migration

When considering positive regulators of NC cell migration two types of molecules can be distinguished: permissive factors that promote motility in a general manner and chemoattractants that drive NC cells to specific locations. Molecules that support migration, such as components of the extracellular matrix, or increase motility fall into the first category. However, defining a chemoattractant is more complicated. We believe that putative attractants should meet three criteria to be classified as such. First, the candidate factor should be expressed in the target tissue. Second, its loss should lead to cell dispersion with cells expressing the receptor for this molecule having a broader distribution than in the control situation. Finally, a localized source of the tested attractant should lead to directional movement as assessed by time-lapse cinematography in vitro and in vivo. The results presented hereafter summarize the data published as they were presented by their authors. However, it should be noted that, so far none of the proposed NC chemoattractants meets all three criteria suggested above.

Alongside the repressive factors and physical barriers preventing NC cells to enter specific regions of the head, several positive regulators have been described (Figs. 7A–C). Members of the VEGF (McLennan et al., 2010), FGF (Kubota and Ito, 2000; Trokovic et al., 2005) and PDGF (Ho et al., 1994; Le Douarin and Kalcheim, 1999; Orr-Urtreger and Lonai, 1992; Orr-Urtreger et al., 1992; Richarte et al., 2007; Schatteman et al., 1992; Smith and Tallquist, 2010; Takakura et al., 1997; Tallquist and Soriano, 2003) families of growth factors are expressed in various places in regions of the head and neck including the branchial arches, and the oral and nasal cavities. FGF and VEGF signaling are essential for the homing of NC cells in the second branchial arch (BA2) in mouse (Trokovic et al., 2005) and chick (McLennan et al., 2010) respectively. However, FGF signaling through FGFR1 seems to act non-cell autonomously by creating a permissive environment in BA2. Additionally, it has been suggested that FGF2 and FGF8 are chemotactic factors for mesencephalic and cardiac NC cells respectively (Kubota and Ito, 2000; Sato et al., 2011), but their chemotactic activity has not been unequivocally demonstrated. PDGF signaling is broadly involved in NC development (Smith and Tallquist, 2010) and embryos with impaired PDGF signaling show various phenotypes including cleft palate, cranial bones defects and ventricular septal defects among other cardiac defects (Morrison-Graham et al., 1992; Robbins et al., 1999; Schatteman et al., 1992; Smith and Tallquist, 2010; Soriano, 1997; Stoller and

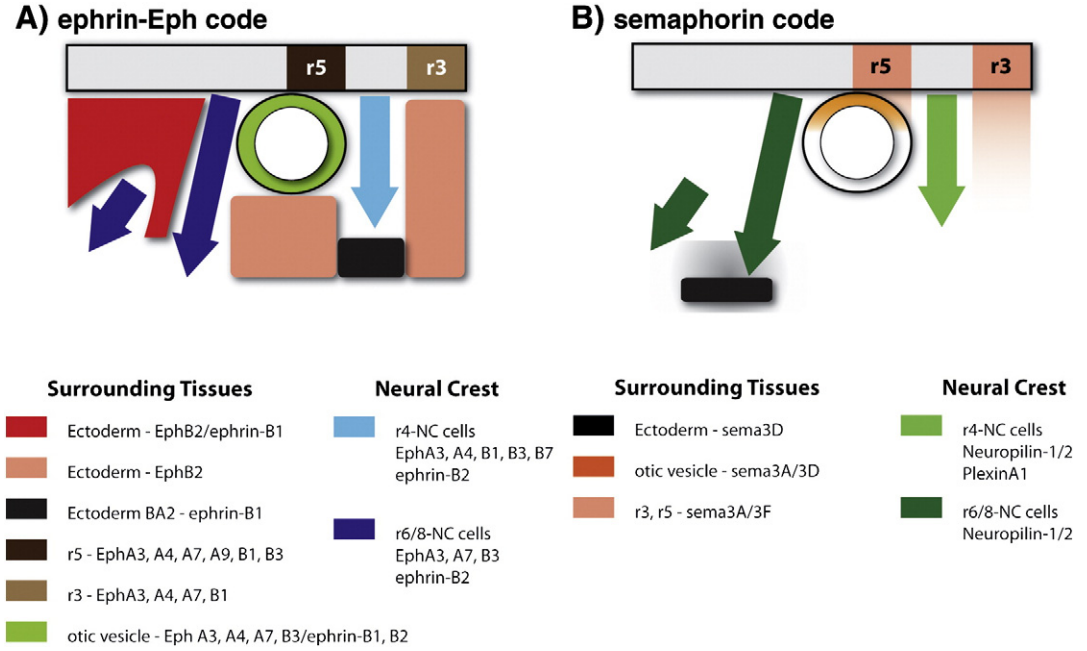

Fig. 5. Ephrin and semaphorin codes regulating the formation of NC-free spaces in the hindbrain of the chick embryo. (A) Distribution of ephrins and Eph receptors in NC cells (arrows) and their surrounding tissues. NC cells express a complex repertoire of ephrins and Ephs. Areas that are not invaded by NC cells mostly contain ephrin-B1 and Eph-B2. Summarized after Baker and Antin (2003) and Mellott and Burke (2008). (B) Distribution of Semaphorins and Neuropilin–Plexin receptors in NC cells and their surrounding tissues. NC cells express Neuropilins 1 and 2 with the addition of plexin-A1 in r4-NC cells. The odd-numbered rhombomeres express semaphorins 3A and 3F, the otic vesicle expresses 3A and 3D and finally the ectoderm ventral to the third stream expresses semaphorin 3D. While the inhibitory function of 3A and 3F has been assessed, the role of 3D remains unknown. Class3-semaphorins are secreted molecules. Their putative diffusion is represented as gradients of the corresponding color. Summarized from Bao and Jin (2006), Eickholt et al. (1999), Gammill et al. (2007), and Osborne et al. (2005).

Epstein, 2005; Tallquist and Soriano, 2003). However, it remains unclear if these effects are due to problems of migration, survival or differentiation of the NC cells.

In addition to VEGF, PDGF and FGF signaling, the chemokine Stromal cell-derived factor 1 (Sdf1 or CXCL12) is expressed in the head at the time of cephalic NC cell migration in *Xenopus*, zebrafish, and chick and one of its receptors, Cxcr4, is expressed by the cephalic NC cells (Olesnicky Killian et al., 2009; Rehimi et al., 2008; Theveneau et al., 2010; Yusuf et al., 2005). Sdf1 has been well characterized as an attractant for various migratory cell populations such as the gastrulating mesoderm (Fukui et al., 2007), germ cells (Blaser et al., 2005; Boldajipour et al., 2008; Doitsidou et al., 2002), posterior lateral line (David et al., 2002; Haas and Gilmour, 2006), lymphocytes (Aiuti et al., 1997; Bleul et al., 1996) as well as stem cells and cancer cells (Dewan et al., 2006; Koizumi et al., 2007; Kucia et al., 2004, 2005a, 2005b). In zebrafish, Sdf1 is required for cranial NC cell migration but the formal demonstration of its role as a chemoattractant has not been undertaken (Olesnicky Killian et al., 2009). In *Xenopus*, Sdf1/Cxcr4 signaling is essential for cephalic NC migration in vivo (Theveneau et al., 2010). In this animal model, local sources of Sdf1 are sufficient to attract NC cells in vitro and in vivo. In NC cells exposed to Sdf1, Cxcr4 signaling stabilizes cell protrusions through activation of the small GTPase Rac1 (Fig. 7C). Although Sdf1 is likely to be the best candidate for a NC chemoattractant (Theveneau et al., 2010); it still does not meet all criteria. It is expressed along each of the migratory pathways, and its inhibition leads to a blockage of NC migration and not to cell dispersion (Olesnicky Killian et al., 2009; Theveneau et al., 2010), as it would be expected for a true chemoattractant. In conclusion, although there is strong evidence for some of the molecules mentioned above to control NC migration by chemotaxis, examples are isolated and the problem is not fully solved. Similar caveats apply to putative chemoattractants discussed in the following section on trunk NC cell migration. Therefore, it is possible that all the NC chemoattractants described so far, work by promoting non-directional migration or chemokinesis instead of chemoattraction, and that this random migration of individual cells leads to directional migration of the cell population, as it has been proposed for mesodermal cells (Benazeraf et al., 2010).

Finally, Cadherin-11 is expressed in *Xenopus* NC cells (Vallin et al., 1998). Its ADAM13-dependent cleavage is essential for *Xenopus*NC cell migration (Borchers et al., 2001; McCusker et al., 2009). Cadherin-11 localizes in the filopodia and binds to Trio, a Guanine nucleotide Exchange Factor, suggesting that it might modulate Rho GTPases and contribute by establishing or reinforcing cell polarity (Kashef et al., 2009). The cleaved form of Cadh-11 can still bind to β-catenin but cannot engage in cell–cell adhesion complexes. The respective functions of the full length and cleaved Cadherin-11 remain to be clarified and the role of the fragment released after cleavage is still unknown.

Molecular control of trunk neural crest cell migration

Migration along the ventromedial pathway

The migration of trunk NC cells using the ventromedial pathway to prescribed, segmented pathways is under the control of several inhibitory cues (Fig. 6A). In mouse, chick and rat, migratory trunk NC cells are restricted to the anterior sclerotome and express EphA/B receptors while the posterior sclerotome expresses ephrin-B ligands (Baker and Antin, 2003; De Bellard et al., 2002; Krull et al., 1997; Santiago and Erickson, 2002; Wang and Anderson, 1997). Inhibition of the ephrin pathway leads to ectopic migration through the posterior sclerotome. Furthermore, semaphorins 3A and 3F are expressed in the posterior sclerotome of chick and mouse NC cells. Inhibition of Sema3F/Nrp2 signaling in chick and mouse leads to unsegmented migration of trunk NC cells but the final patterning of the ganglia is not affected (Gammill et al., 2006). Inhibition of Sema3A/Nrp1 signaling on the other hand leads to ectopic sympathetic ganglia and accumulation of NC cells in the intersomitic space (Schwarz et al., 2009). Joint inhibition of Sema3A and 3F leads to a complete loss of metameric distribution of NC cells and fusion of ganglia (Schwarz et al., 2009). The role of these pathways in *Xenopus* and zebrafish embryos, where

trunk NC cells migrate along the caudal and medial somite respectively, has not been assessed.

In addition to ephrin and semaphorin signaling, F-spondin (Debby-Brafman et al., 1999) and Versicans (Dutt et al., 2006; Perissinotto et al., 2000; Perris et al., 1996), two components of the extracellular matrix, are also expressed in the caudal sclerotome and in the vicinity of the notochord. Blocking F-Spondin using antibodies leads to ectopic NC cell migration in the caudal sclerotome in vivo (Debby-Brafman et al., 1999) suggesting an inhibitory function. The effect of versican on neural crest migration is not completely understood. Its expression is mainly found outside NC streams but loss of function experiments impair neural crest migration, suggesting a positive role, whereas culture of NC in vitro on stripes of versican suggests an inhibitory activity (Dutt et al., 2006; Perris et al., 1996). The broad role that is generally proposed for the extracellular matrix (ECM) in neural crest migration is a permissive one, with proteins like fibronectin or laminin being essential for cell migration. The participation of the ECM in NC migration, not covered in depth here, has been reviewed elsewhere (Perris and Perissinotto, 2000).

Migration along the ventromedial route is also controlled by Sdf1, although to a lesser extent than at cranial levels. In mouse, Cxcr4 is expressed by NC cells that form the dorsal root ganglia (Belmadani et al., 2005) while in chick it is only expressed by precursors of the sympathetic ganglia (Kasemeier-Kulesa et al., 2010). In both mouse and chick NC cells, perturbing Cxcr4 expression and/or Sdf1 localization impairs the formation of the dorsal root and sympathetic ganglia, respectively.

Finally, NC cells using the ventral pathway express Robo receptors and are exposed to Slit ligands (De Bellard et al., 2003; Jia et al., 2005). Slit/Robo signaling selectively prevents trunk NC cells from entering the gut while allowing vagal NC cells to do so. In addition, despite preventing their migration along the gut, Robo signaling promotes overall motility of ventrally migrating trunk NC cells.

Migration along the dorsolateral pathway

Migration of trunk NC cells along the dorsolateral pathway is controlled by ephrin/Eph, endothelin and Slit/Robo signaling (Figs. 6A–B). In chick, while trunk NC cells on the ventromedial route express EphB3 and are repelled by ephrin-B1 present in the dorsolateral path, cells restricted to the melanocytic lineage upregulate EphB2 and respond positively to ephrin-B1, which stimulates their migration under the dorsal ectoderm (Santiago and Erickson, 2002). Similarly, the dorsolateral route contains endothelins, neuronal and glial precursors on the ventromedial path express endothelin receptor B (EDNRB), while melanocytic precursors express endothelin receptor B2 (EDNRB2) (Harris et al., 2008; Lee et al., 2003; Pla et al., 2005; Shin et al., 1999). EDNRB prevents entry onto the dorsolateral path while EDNRB2 promotes migration onto the dorsolateral pathway (Harris et al., 2008; Pla et al., 2005). Finally, trunk NC cells express the receptors Robo1 and 2. When a dominant-negative Robo receptor is overexpressed in the NC cells, there is premature invasion of NC cells onto the dorsolateral path (Jia et al., 2005).

In chick and mouse, restriction to the melanoblastic lineage is key to entry onto the dorsolateral path (Harris and Erickson, 2007; Kelsh et al., 2009). However, in *Xenopus*, only a small portion of melanocytes precursors migrate through the dorsolateral route. Most of the presumptive melanocytes use the ventromedial pathway together with glial and neuronal precursors and then move laterally, underneath the somites, to reach the epidermis (Collazo et al., 1993). In zebrafish the melanocyte precursors use both ventral and dorsolateral pathways equally but other pigment cells show specific preferences for one path or the other (Kelsh et al., 2009). It remains to be determined if these ventrally migrating melanocytes in fish and frogs are restricted later into the melanoblastic lineage and therefore cannot enter the dorsolateral path soon after delamination or if the entry under the dorsal ectoderm is controlled in a different manner in this species.

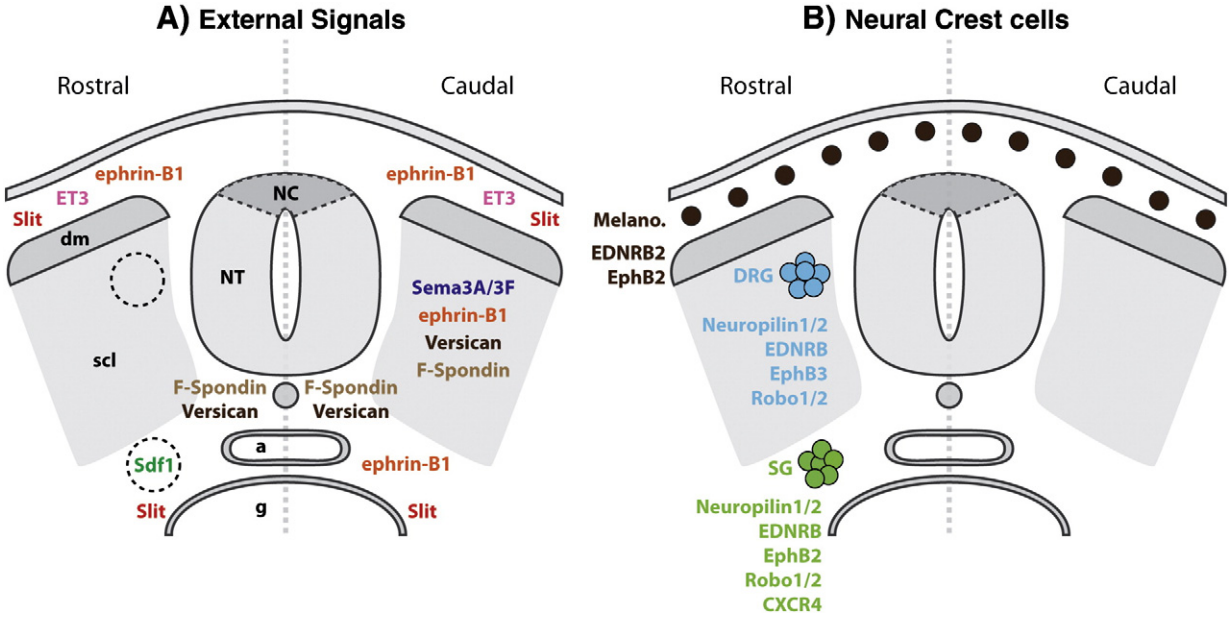

Fig. 6. Molecular control of early trunk NC cell migration in the chick embryo. (A) Distribution of signaling molecules involved in trunk NC guidance at the rostral and caudal levels of one somite. The anterior half of the sclerotome is free of inhibitors while the posterior part contains members of ephrin and semaphorin families and inhibitory extracellular matrix molecules such as Versicans and F-Spondin which altogether contribute to restrict NC cell migration to the anterior half. All along the antero-posterior axis, the dorsolateral path and the notochord contain inhibitory factors including Slit ligands, endothelin-3 (ET-3) and ephrin-B1. Interestingly, inhibitors present in the dorsolateral pathway are inhibitory for the ventrally migrating crest but permissive for or non effective on the melanocytes precursors using this route. In addition, the surroundings of the gut contain Slit ligands which prevent entry of trunk NC cells but are permissive for enteric crests. Finally, the chemoattractant Sdf1 is expressed in the anlagen of the sympathetic ganglia, where it specifically attracts Cxcr4 positive-NC cells. (B) Distribution of the different subpopulations of trunk NC cells at rostral and caudal somitic levels. Differential expressions of receptors of Eph, Robo, Endothelin and Neuropilin families and/or Cxcr4 expression govern the targeting of the different subpopulations to specific locations. See text for references. Dorsal root ganglion and sympathetic ganglion anlagen are shown as circular dotted lines. a, aorta; dm, dermomyotome; DRG, dorsal root ganglion; g, gut; Melano., melanocytes; NT, neural tube; NC, pre-migratory NC cells; scl, sclerotome; SG, sympathetic ganglion.

Finally, in mouse, melanocytes progressively abandon the skin to accumulate in the hair follicle (Kelsh et al., 2009) and this final migration is controlled by Sdf1 (Belmadani et al., 2009). It would be interesting to see if in the chick, where melanocytes colonize both the skin and feathers, additional mechanisms occur to maintain a pool of pigment cells in the epidermis.

Cell–cell interactions and signal integration during neural crest cell migration

Numerous external cues may be involved in the patterning of the discrete migratory streams but the directionality of NC cell migration cannot simply emerge from a balance of inhibitors creating NC-free zones and attractants promoting invasion of specific regions. Inhibitors can restrict cell migration from certain areas but cannot give directionality. In addition, the putative NC chemoattractants identified so far are not precisely expressed by the NC target tissue, as would be expected for a chemoattractant, but rather widely spread along migratory pathways. Moreover, these migratory routes are very long and it is unlikely that a NC chemoattractant expressed in the target tissue could be sensed by cells delaminating from the dorsal neural tube located several hundreds of micrometers away. Therefore, it is more likely that directionality is regulated on a local scale and that additional mechanisms are required to generate and modulate it.

Interestingly, some of the earliest observations of neural crest migration in vitro demonstrated the intrinsic high directionality of these cells (Davis and Trinkaus, 1981), suggesting that external signals are not essential for neural crest directional migration. However, it now appears that cell–cell interactions between NC cells of the same stream massively contribute to the generation of cell polarity, overall directionality and the ability to read external signals.

Cell–cell interactions and polarity

Events that could lead to directional cell migration in the absence of external signals are long-lasting cell–cell contacts and transient cell collisions mediating Contact Inhibition of Locomotion (CIL). CIL is the process by which a cell ceases migrating upon contact with another cell, described by Abercrombie (Abercrombie and Dunn, 1975; Abercrombie and Heaysman, 1953). At low cell density, CIL leads to a change in the direction of migration upon collision, while at high cell density only cells exposed to a free edge can migrate away from the cluster leading to the directional migration of the whole group (Mayor and Carmona-Fontaine, 2010). The idea that CIL could be the driving force of NC migration has a long history (Erickson, 1985), but only recently has this mechanism been demonstrated for the in vivo migration of zebrafish and *Xenopus* NC (Carmona-Fontaine et al., 2008b). Some have argued that such mechanism could only account for dispersion but not mass migration (Thomas and Yamada, 1992). Observations made in vitro by Thomas and Yamada suggested that NC cell motility is improved by contact with other cells, a phenomenon coined as contact stimulation of cell migration. Their results show that isolated NC cells exhibit poor motility; whereas NC cells cultured at higher cell density migrate extensively. In a series of studies using high resolution time-lapse microscopy in the chick embryo, Kulesa and colleagues revealed that cephalic NC cells maintain short and long-range cell–cell interactions during migration (Kulesa and Fraser, 1998, 2000; Teddy and Kulesa, 2004) confirming previous in vitro observations (Erickson, 1985). It was noted that most migratory NC cells are engaged in chains rather than moving as individual cells (Fig. 7B), in a similar fashion as heart fibroblast cultured in vitro, which exhibit CIL (Ambrose, 1961). Kulesa and colleagues have elegantly described cell–cell interaction between NC with two possible outcomes. After contact, cells could either move away from each other or the follower cell may pause for a while before resuming migration towards the leader cell. In both cases, the contact was directly followed by a retraction of the cell protrusions (Fig. 7B red inhibitory arrows) indicating that contact-inhibition does take place when two chick NC cells collide. It was also observed that cells in chains had a higher directionality than cells wandering around as single cells suggesting that cell–cell interactions promote the overall directional migration of NC cell groups (Fig. 7B). These in vivo data were reminiscent of CIL and contact stimulation of cell migration, supporting a role for cell–cell contacts and the idea of a certain degree of collectiveness during NC cell migration. However, the fact that cell collisions leading to protrusion collapse can improve directional migration of a group of NC cells suggests that the contact stimulation of cell migration observed by Thomas and Yamada was not different from CIL but rather the outcome of CIL taking place at high cell density. The molecules involved in the cell–cell contacts in chick cephalic NC cells that mediate protrusions collapse and/or chain formation remain unknown.

A role for CIL in migratory NC cells was specifically demonstrated in vivo using *Xenopus* and zebrafish cephalic NC cells (Carmona-Fontaine et al., 2008b). CIL acts at two levels. Upon collision, NC cells retract their cell protrusions, repolarize, and move away from each other. In dense groups, CIL prevents cells from overlapping by preventing the formation of cell protrusions at the region of cell–cell contact and therefore restricting the protrusions to the free edge (Fig. 7A, red inhibitory arrows; Fig. 8A). In *Xenopus*, CIL is mediated by an N-Cadherin-dependent cell–cell interaction that triggers the non-canonical Wnt/Planar cell polarity pathway (PCP) (Carmona-Fontaine et al., 2008a, 2008b; De Calisto et al., 2005; Matthews et al., 2008a; Theveneau et al., 2010). N-Cadherin–Wnt/PCP control the activity levels of the small GTPases RhoA and Rac1 at the cell–cell contacts (Figs. 8A and 9; Carmona-Fontaine et al., 2008b; Theveneau et al., 2010; Theveneau and Mayor, 2010). RhoA is involved in cell contractility, formation of stress fibers, and in defining the back identity of migratory cells whereas Rac1 is involved in membrane ruffling, cytoskeleton dynamics and is a key regulator of the formation and the stability of the cell protrusions (Ridley and Hall, 1992; Ridley et al., 1992, 2003). Consequently, when N-Cadherin and/or Wnt/PCP are impaired NC cells fail to undergo CIL and produce ectopic protrusions on top of each other (Carmona-Fontaine et al., 2008b; Theveneau et al., 2010). However, such CIL-driven migration would lead to a complete dispersion of the cell population.

Interplay between cell–cell interactions and chemotaxis

Interestingly, by inducing polarization of the cells, CIL has a direct influence on their ability to undergo chemotaxis (Theveneau et al., 2010). More specifically, groups of NC cells respond very efficiently to the external chemoattractant Sdf1. In groups, cells are polarized due to cell interactions/CIL (Fig. 8A). Then protrusions facing high concentration of attractant are further stabilized. This biases the group directionality toward the source of the attractant (Fig. 8B). In contrast, isolated NC cells only show a poor chemotactic response (Theveneau et al., 2010). However, when cultured at high cell density, allowing frequent collisions, individual NC cells regain the ability to respond efficiently to chemotactic signals. This collective chemotaxis depends on CIL and is dramatically impaired by N-Cadherin loss-of-function (Theveneau et al., 2010). In addition, cell–cell adhesion taking place between NC cells is on occasion sufficient for non-motile cells (including dividing cells) to be passively pulled by their motile neighbors (Theveneau et al., 2010). Therefore, the interplay between CIL and chemotaxis and the maintenance of some level of cell–cell adhesion required for CIL and cell pulling can explain the biased dispersal of the NC cell population towards region where Sdf1 is expressed. This may be especially true for the early phase of migration when N-Cadherin levels at the cell contacts are high and cells display an epithelioid shape (Theveneau et al., 2010). The role of N-Cadherin in contact-mediated polarity and chemotaxis has not been assessed in zebrafish but the fact that both N-Cadherin and Sdf1 signaling are required for NC cell migration in fish suggests a similar role (Olesnicky Killian et al., 2009; Piloto and Schilling, 2010). Interestingly,

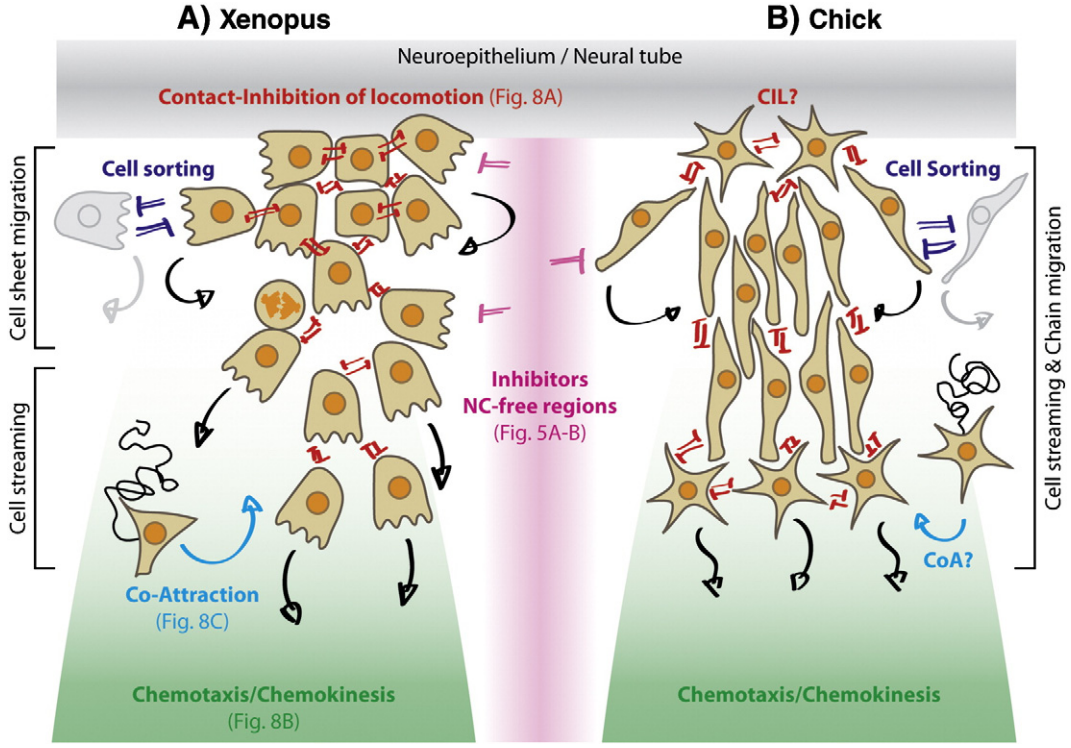

Fig. 7. Cell–cell interactions and external signals regulating collective cell migration of cephalic NC cells. (A) *Xenopus* cephalic NC cells start migrating as a cell sheet. Cells located at the border of the population exhibit a clear cell polarity with cell protrusions oriented towards the outside. On the contrary, cells inside the population that are completely surrounded by other NC cells show no obvious polarity and display only cryptic protrusions. As migration proceeds the population becomes more mesenchymal and migration turns into a cell streaming. Cell–cell contacts in groups or between single cells trigger Contact-Inhibition of Locomotion (CIL, red inhibitory arrows) which leads to the collapse of cell protrusions. CIL, through its effect on cell polarity, is essential for coordinated migration and sensing of external cues. Cells that lose contacts with other cells have poor chemotactic response (tortuous path) but are actively attracted back towards other NC cells by co-attraction (blue arrows). Modified after Theveneau et al. (2010) and Carmona-Fontaine et al. (2011). See main text for details. (B) Chick cephalic NC cells undergo cell streaming and chain migration. Collisions between cells lead to the collapse of cell protrusions reminiscent of CIL (red inhibitory arrows) and a gathering behavior reminiscent of CoA (blue arrows). Modified after Teddy and Kulesa (2004). In both *Xenopus* and chick isolated cells migrate less efficiently than cells in groups or chains (shown as tumultuous paths). NC cells at the border of a stream may encounter NC cells from an adjacent stream (gray cells) but differential expressions of ephrin/Eph molecules prevent mixing. In addition, inhibitors (ephrins/Eph, class3-semaphorins) present in the surrounding tissues (shades of pink) induce the collapse of cell protrusions and restrict NC migration to specific routes. Finally, chemotactic and chemokinetic factors promoting motility and targeting NC cells to specific locations are shown as shades of green.

the zebrafish posterior lateral line primordium, another collectively migrating cell population whose migration depends on Sdf1 (Dambly-Chaudiere et al., 2007; David et al., 2002; Haas and Gilmour, 2006; Valentin et al., 2007), also requires proper N-Cadherin contacts to successfully migrate (Kerstetter et al., 2004).

Besides cadherin-based junctions, migratory cephalic NC cells also establish gap junctions (Bannerman et al., 2000; Huang et al., 1998; Lo et al., 1997; Waldo et al., 1999; Wang et al., 2010; Xu et al., 2006) whose presence influences their polarity and survival. Just as N-Cadherin contacts improve the response to Sdf1, gap junctions affect NC cells' ability to polarize and read external signals such as semaphorins (Xu et al., 2006). This suggests that, in groups, general competence to respond to external signals is controlled in a contact-dependent manner. Such a mechanism would give an advantage to groups over single cells and favors collective against solitary cell migration (for discussion see Theveneau and Mayor, 2011a). The link between the gap junctions and cadherin-based contacts has not been fully addressed, but previous work suggests that they could work together or through parallel pathways (Xu et al., 2001a, 2001b).

Later on, when NC cells reach the ventral region of the head, they display a more mesenchymal morphology and have fewer contacts (Sadaghiani and Thiebaud, 1987; Theveneau et al., 2010), but still remain in close proximity. Notably, NC cells located at the back of a stream do not migrate backward to fill the gap that is generated between the NC cells and the neural tube. This indicates that additional mechanisms have to compensate for the progressive loss of long-lasting cell–cell contacts.

Integration of CIL-based dispersion and mutual attraction during collective cell migration of NC cells

Interestingly, *Xenopus* NC cells exhibit mutual attraction (Carmona-Fontaine et al., 2011). NC explants placed in close proximity attract each other from a distance while cells that detach from a cluster consistently move back to rejoin the group (Fig. 7A, blue arrows). This co-attraction behavior is mediated by the complement factor C3a and its receptor C3aR which are co-expressed in migratory *Xenopus* cephalic NC cells (Carmona-Fontaine et al., 2011). Each NC cell secretes C3a and therefore individual cells that leave a group are attracted towards regions of higher cell density where the local concentration of C3a builds up (Fig. 8C). C3a/C3aR signaling leads to Rac1 activation which polarizes the cells (Fig. 8C). Co-attraction (CoA) prevents cell dispersion by attracting NC cells toward each other and thus appears as an opposite force to CIL. However, the fact that cells are constantly attracted to each other also promotes collisions and establishment of a new cell polarity through CIL (Fig. 8D). With CIL alone cells would quickly disperse and, when physical contact is lost, CIL cannot promote cell polarity anymore. Thus, mutual attraction, by preventing excessive dispersion, helps to maintain cell density and, therefore positively feedbacks into CIL by promoting cell collisions when cells gather. It should be noted that while a loss of cell contacts impairs chemotaxis towards Sdf1, cell dissociation does not affect chemotaxis towards C3a. This suggests that CXCR4 availability may be regulated in a cell–cell interaction dependent manner while C3aR may not. This remains to be investigated. In addition, direct binding between Ca3 and Sdf1 and interaction

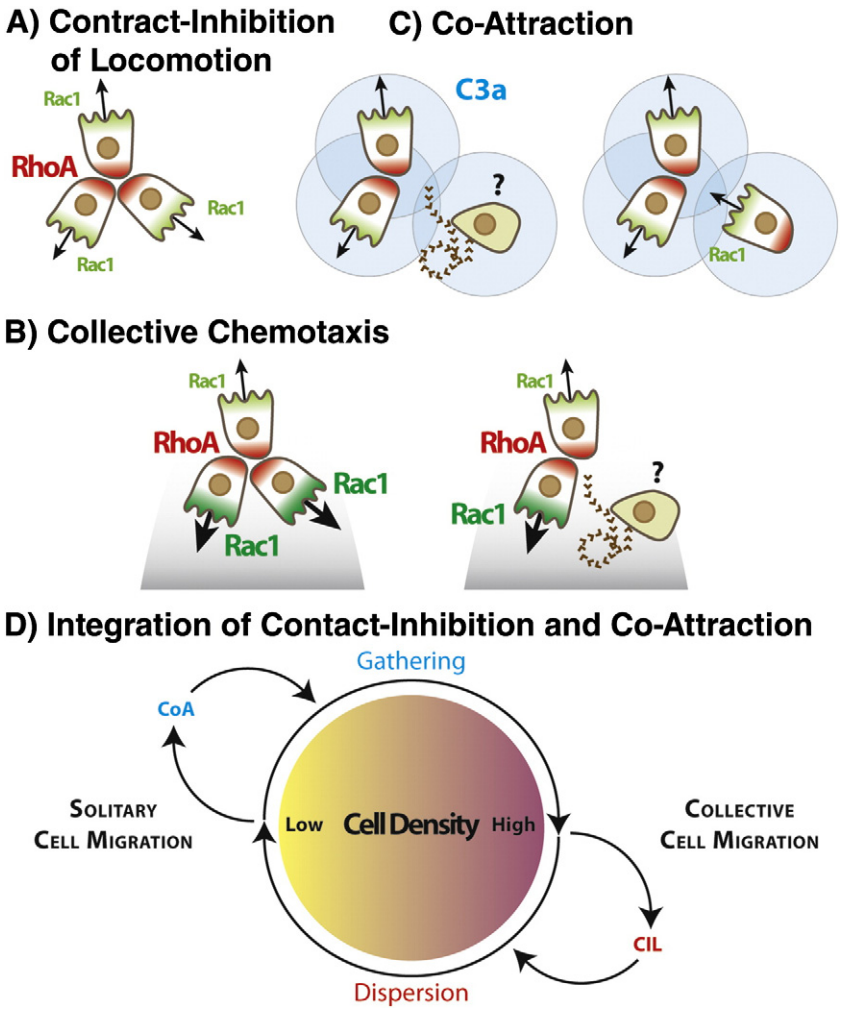

Fig. 8. Contact-Inhibition, chemotaxis and Co-Attraction cooperate to promote collective migration in *Xenopus* cephalic NC cells. (A) NC cells are polarized due to cell–cell interactions mediating Contact-Inhibition of Locomotion (CIL). They show high RhoA activity at the contact and high Rac1 at the free edge. (B) External attractant further stabilizes well-oriented protrusions (increased Rac1 activity) creating a directionality bias towards region of high concentration of attractant. Cells that detach from the cluster transiently lose polarity (brown cell) and are unable to read external attractant. (C) Each NC cell is secreting C3a (blue circles) which acts as a local attractant promoting co-attraction (CoA) and gathering of NC cells. (D) CoA compensate for cell dispersion induced by CIL but also positively feedbacks into CIL by promoting cell collisions while cells are gathering back together. Altogether CIL and CoA help NC cells to undergo collective cell migration while retaining mesenchymal properties.

between C3aR and CXCR4 have been documented (Honczarenko et al., 2005; Reca et al., 2003; Shinjyo et al., 2009; Wysoczynski et al., 2007) suggesting that both C3a and Sdf1 signaling pathways may be modulating each other. Such interaction has yet to be found in NC cells. Lastly, ectopically expressing C3a and C3aR into cells that normally migrate as individual cells, such as myeloid cells, is sufficient to promote collective migration (Carmona-Fontaine et al., 2011). Altogether, the interplay between CIL and CoA allows NC cells to undergo collective cell migration while retaining mesenchymal properties.

Finally, in addition to cell–cell adhesion and mutual attraction, the fact that each NC stream is surrounded by inhibitors (Figs. 7A–B, shades of pink, see also Figs. 5 and 6) and cannot mix with NC cells form an adjacent stream (Figs. 7A–B, gray cells, purple cell sorting arrows) also helps to maintain a high cell density and ensure a high rate of polarizing cell collisions (for discussion see Theveneau and Mayor, 2011b).

Signal integration

Migrating NC cells are exposed to a wide range of signals and there is extensive crosstalk between different signaling pathways (Fig. 9). The data described above are consistent with the possibility that Rho GTPases, as key regulators of cell motility, are likely to be common downstream effectors of multiple signaling events (Fig. 9 and for discussion see Theveneau and Mayor, 2010). In addition, it appears that several signaling pathways share common receptors. Neuropilin-1, for instance, can act as a co-receptor for class3-semaphorins, VEGF and PDGF ligands (Bachelder et al., 2003; Eickholt et al., 1999; Evans et al., 2011; Lwigale and Bronner-Fraser, 2009; McLennan et al., 2010; Pellet-Many et al., 2011). Interestingly, Syndecan-4, a proteoglycan capable of interacting with Fibronectin and Sdf1 and that can work as a co-receptor for G-protein coupled receptors (Carey, 1997; Charnaux et al., 2005; Matthews et al., 2008b), is also required for *Xenopus* and zebrafish cephalic NC cell migration (Matthews et al., 2008b). Syndecan-4 helps generate cell polarity and directional migration by inhibiting Rac1 activity. However, since Syndecan-4 also has the ability to bind Sdf1, it could act as a co-receptor for Cxcr4 and promote Rac1 activation upon exposure to Sdf1 (Fig. 9). Finally, protein tyrosine kinase 7 (PTK7) is involved in PCP signaling and acts as a co-receptor for Plexin-A1 in *Xenopus* cephalic NC cells (Shnitsar and Borchers, 2008; Wagner et al., 2010), suggesting that it may be involved in CIL and semaphorin signaling.

Altogether these observations suggest that NC cells take decisions based on the information available at a given time and that their competence to respond depends on their ability to interact with

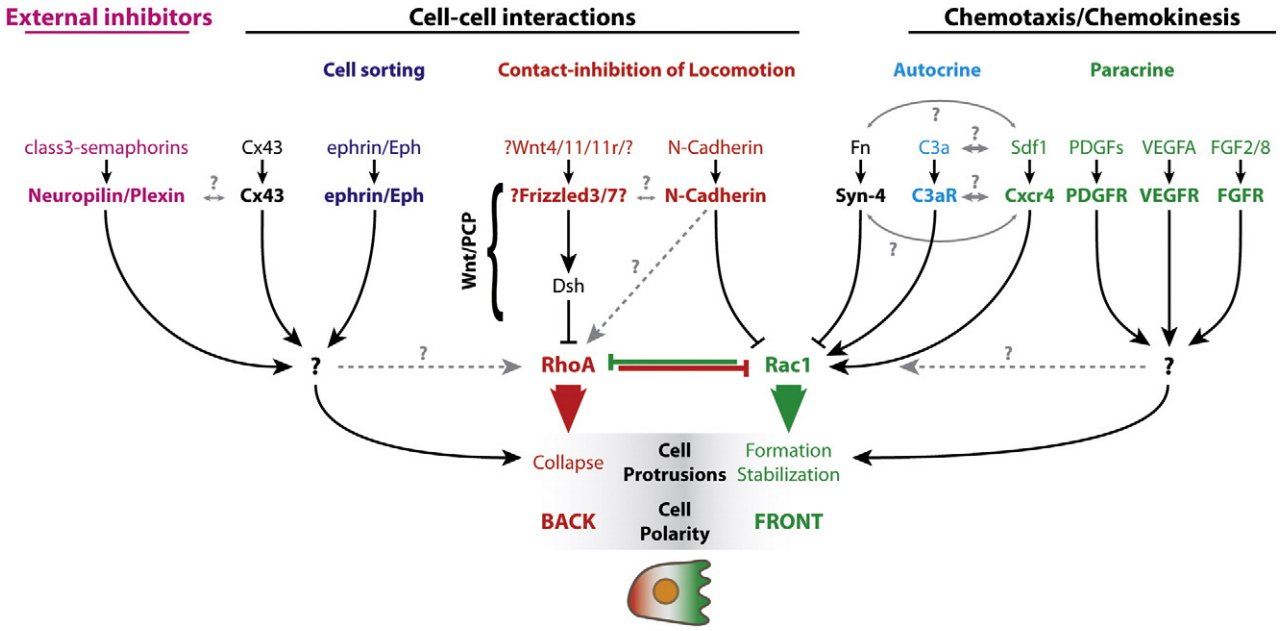

Fig. 9. Signal integration. Summary of the different classes of signaling pathways involved in regulating cephalic NC cell motility and polarity. External inhibitors produced by surrounding tissues are here represented by semaphorins. Cell–cell interactions include: ephrin/Eph signaling among NC cells and between NC cells and their surrounding tissues; but also GAP junctions (Cx43) and CIL (Wnt/PCP, Cadherins) among NC cells. Semaphorin and ephrin signaling promote the collapse of cell protrusions, possibly through RhoA activation. Connexin-43 (Cx43)-based GAP junctions are required for NC cells to polarize upon cell contacts and to interpret semaphorin signaling. How this effect is mediated remains unknown. CIL relies on PCP signaling and N-Cadherin-based cell–cell contacts. CIL promotes RhoA activity and blocks Rac1. Syndecan-4 inhibits Rac1. Paracrine chemokinetic/chemotactic factors include Sdf1, VEGFA, FGF2/8 and PDGFs. Sdf1/Cxcr4 signaling activates Rac1. Downstream effectors of PDGF, VEGF and FGF pathways responsible for their positive effect on NC cell migration are unknown but likely to eventually regulate the small Rho GTPases. Autocrine signals are represented by complement factor C3a and its cognate receptor C3aR. C3a/C3aR signaling activates Rac1. Many crosstalks are likely to take place between pathways as several common effectors can be found. Neuropilin-1 can act as co-receptor for Plexins, VEGFR and PDGFR. Syndecan-4 (Syn-4) binds to Sdf1 and Fibronectin (Fn) and can act as a co-receptor for Cxcr4. C3a and Sdf1 can bind to each other while CXCR4 and C3aR can interact. Please note that data from *Xenopus*, chick, mouse and fish embryos are mixed in this figure. See main text for details and references.

other NC cells and on the precise ratio of surface receptors at the time of the decision (Fig. 9).

It is important to note that most of the data on cell–cell interactions and signal integration during NC cell migration come from cephalic NC cells. Nevertheless, trunk NC cells also migrate in large numbers, remain in very close proximity and even form chains as observed when traveling through the sclerotome in chick (Kasemeier-Kulesa et al., 2005). In addition, Wnt/PCP is required for directional migration of the trunk NC cells in zebrafish and chick embryo (Matthews et al., 2008b; Rios et al., 2011). Therefore, even if CIL and cell cooperation have not been formally assessed, it seems very likely that mechanisms similar to the ones described for cephalic NC cells are at work in the trunk (for discussion see Theveneau and Mayor, 2011a). Finally, heterotypic contact-inhibition has been observed between early migrating trunk NC cells in zebrafish and somitic cells (Jesuthasan, 1996). It appears that the first wave of fish NC cells collapses protrusions when contacting somitic cells whereas late emigrating NC cells that enter the dorsolateral path do not. The molecules involved in this process are unknown.

In summary, evidence in chick, zebrafish and *Xenopus* embryos indicates that cell–cell interactions, and contact inhibition of locomotion in particular, are two of the important driving forces of directional migration (Figs. 7A–B, 8A–D). Cell–cell contacts polarize neural crest cells, allowing them to efficiently respond to external guidance cues. At the same time, negative signals that restrict neural crest migration into streams and mutual attraction counterbalance the cell dispersion promoted by CIL. These signals maintain NC cells at a high cell density increasing the probability of cell collisions which constantly repolarize the cells (Figs. 7A–B, 8A–D) (Barlow et al., 2008; Carmona-Fontaine et al., 2011; Theveneau and Mayor, 2010, 2011b; Theveneau et al., 2010). It seems that all these signals activate different pathways that eventually converge in giving neural crest cells the polarity to move in the correct direction (Fig. 9).

A role for NC cell migration in patterning surrounding tissues

NC cells delaminate all along the rostrocaudal axis and shortly thereafter are partitioned by environmental influences into discrete streams at both cephalic and trunk levels. This early patterning is essential to properly position ganglia of the peripheral nervous system that are close to the central nervous system; such as the cranial ganglia and the dorsal root ganglia. However, this early patterning is on several occasions only transient. In the head, for instance, time-lapse movies show that cells moving on either side of the otic vesicle interact, and occasionally change streams, after they have passed this structure (Kulesa and Fraser, 2000). More impressive is the situation of the trunk NC cells forming the dorsal root and sympathetic ganglia. NC cells that form these ganglia are initially targeted to distinct anlagen but some mixing does take place along the dorso-ventral axis to refine the distribution of NC cells between the two ganglia (Goldstein and Kalcheim, 1991; Kasemeier-Kulesa et al., 2005). Furthermore, sympathetic ganglia precursors come out of the somites as a segmented population but quickly move anteriorly and posteriorly to mix with adjacent streams of trunk NC cells abolishing the previous pattern. The mixing involves movements that are two-somite wide anteriorly and posteriorly to one given level (Kasemeier-Kulesa et al., 2005; Le Douarin and Kalcheim, 1999; Yip, 1986). NC cells will then be separated again as discrete ganglia by ephrin-based signaling and N-Cadherin-dependent cell adhesion (Kasemeier-Kulesa et al., 2006). Each sympathetic ganglion contains NC cells coming from 4 to 5 adjacent somitic levels. By contrast dorsal root ganglia, that form in the anterior part of the sclerotome, are made of NC cells from only two adjacent somitic levels (Teillet et al., 1987).

One intriguing question raised by the above observations, is why go to so much trouble to generate an early patterning only to reshuffle the NC cells soon after? Publications describing patterning defects of NC cell migration usually focus on the impact on the final organization

of NC-derived structures. The putative role of the migratory NC population as a signaling population is generally overlooked. One possibility is that migratory NC cells are signaling to their surrounding tissues while on the move and that the patterning of their migratory routes is crucial to position the signals coming from the NC cells. Much work remains to be done on signals from the NC cells and their influence on local tissues. But experiments done at cephalic levels on NC cells and brain development and at trunk levels on the interaction between migratory NC cells and myogenic precursors suggest that exciting new concepts may come from such studies (Creuzet et al., 2006; Etchevers et al., 1999; Le Douarin et al., 2007; Rios et al., 2011; Van Ho et al., 2011 and see chapter by LeDouarin et al., this volume).

Neural crest and cancer

NC cells and malignant tumour cells show striking similarities in terms of gene expression and general behavior (Kuriyama and Mayor, 2008; Nieto, 2009; Thiery et al., 2009). More precisely, cancer cells often show high levels of TGFβ, Wnt and various receptor tyrosine kinase signaling (Thiery and Sleeman, 2006) reminiscent of the BMP, Wnt and FGF signals involved in NC induction and the BMP/Wnt cascade triggering EMT (Fig. 10A, see also Fig. 2). These pathways activate the expression of several transcription factors of the Snail, Twist, SoxE, FoxD, and Ets families (Fig. 10B and Barrallo-Gimeno and Nieto, 2005; Dittmer, 2003; Dong et al., 2004; Foubert et al., 2010; Harris et al., 2010; Hsu et al., 2004; Moreno-Bueno et al., 2008; Seth and Watson, 2005; Turner et al., 2007; Wallerand et al., 2009) which are essential for proper NC development and whose expression is upregulated in many cancers. The cocktail of transcription factors gives malignant cancer cells and NC cells the ability to undergo EMT. Among the key events of EMT, a dramatic change of cell–cell adhesion properties is crucial to allow cells to exit their original tissue (Fig. 10C and Berx and van Roy, 2009; Hazan et al., 2004; Maeda et al., 2005; Wheelock et al., 2008). The nature of the cell adhesion molecules expressed by the cells does not matter per se and all sorts of cadherin switches have been observed in cancer cells and during embryogenesis (summarized in Wheelock et al., 2008). Therefore, the important point is that cells undergoing EMT are expressing a combination of cell–cell adhesion molecules that differs from that of their tissue of origin. It should be noted that the switch in cadherin expressions is not total and both cancer and NC cells often maintain some level of their original cadherins after undergoing EMT. Importantly, changes in expression of cell–cell adhesion molecules are only transient in some NC subpopulations with an upregulation of N-Cadherin and N-CAM at the end of migration (Akitaya and Bronner-Fraser, 1992; Duband, 1990; Shiau and Bronner-Fraser, 2009; Thiery et al., 1982b). Therefore, NC is a good system to study the regulation of cell–cell adhesion molecules during EMT and cell migration. Getting information about how cell–cell adhesion is regulated over time may be crucial to design techniques to address this issue in a pathological context. In addition, malignant tumour cells express various MMPs and ADAMs (Egeblad and Werb, 2002; Murphy, 2008; Overall and Kleifeld, 2006; Page-McCaw et al., 2007) which endow them with abilities to digest ECM components and cell surface molecules including cadherins (Fig. 10D). Expression of MMPs and ADAMs in cancer cells is often associated with high invasive potential and poor prognosis (Murphy, 2008; Page-McCaw et al., 2007). The function of these molecules in NC development is poorly understood but NC cells express several members of both MMPs and ADAM families (Fig. 9D), and loss-of-function experiments have shown that their activity is essential for delamination and migration (Alfandari et al., 2001; Duong and Erickson, 2004; McCusker et al., 2009; Shoval et al., 2007). Moreover, NC cells migrate through meshworks of loose ECM or along dense basement membranes and encounter a great diversity of substrates (Perris and Perissinotto, 2000). NC cells can be observed and manipulated in vivo and in vitro suggesting that great insight on the role of MMPs and ADAMs could be obtained using the NC system.

After departing from their original location, both NC and malignant tumour cells undergo solitary and collective cell migration (Deisboeck and Couzin, 2009; Friedl and Gilmour, 2009; Friedl and Wolf, 2009; Khalil and Friedl, 2010; Mayor and Carmona-Fontaine, 2010; Rorth, 2009; Theveneau and Mayor, 2011b; Wolf et al., 2007). Collectiveness in cephalic NC cells is in part due to the autocrine C3a/Ca3R signaling through which NC cells attract each other (Carmona-Fontaine et al., 2011; see Cell–cell interactions and signal integration during neural crest cell migration section of this review). Several tumors such as gliomas show a clear upregulation of various growth factors and their cognate receptors during tumorigenesis (Hoelzinger et al., 2007). Some of these molecules (i.e. FGFs and PDGFs) have clear chemotactic abilities. Therefore, one can imagine that tumour cells with such autocrine signaling may use these signals to promote collectiveness by maintaining high cell density through a mutual-attraction system (for discussion see Theveneau and Mayor, 2011a).

NC cells and metastatic cancer cells display opportunistic behaviors by making use of pre-existing structures (Fig. 10E). For instance, many tumour cells migrate along the nerves and use the blood vessels to disseminate (Nguyen et al., 2009) while NC cells make the most of the basement membrane of the ectoderm and the dermomyotome, and also migrate along nerves (Hall, 2008; Le Douarin and Kalcheim, 1999). Moreover, in both systems, migration and targeting to specific tissues are controlled by external cues. For instance, NC cells are targeted to the anlagen of the dorsal root/sympathetic ganglia and the hair follicle by an Sdf1-dependent mechanism (Belmadani et al., 2005, 2009; Kasemeier-Kulesa et al., 2010) while homing of some cancer metastasis into several organs is also depending on Sdf1/Cxcr4 signaling (Dewan et al., 2006; Kucia et al., 2005b; Nguyen et al., 2009). It also seems that some of the negative regulators of NC migration, such as Semaphorin-3 F, are on some occasion acting as tumour suppressors (Neufeld and Kessler, 2008). When reaching their final destination, NC cells finally stop migrating and undergo differentiation. The arrest of migration is sometimes coupled with a reaggregation process as when NC cells form the ganglia of the peripheral nervous system (Duband et al., 1985; Kasemeier-Kulesa et al., 2006; Lallier and Bronner-Fraser, 1988). Interestingly, secondary tumors, which are established in distant organs by metastatic cancer cells, often show signs of a reversion to a more epithelial state (Nguyen et al., 2009; Polyak and Weinberg, 2009; Thiery et al., 2009) and tumour cells that have the ability to undergo mesenchyme-to-epithelium transition can better survive in newly colonized locations than mesenchymal cancer cells (Polyak and Weinberg, 2009). In addition, EMT also confers stem cell properties on cells (Mani et al., 2008; Morel et al., 2008; Polyak and Weinberg, 2009) which could be lost upon reversion to a more epithelial state. Altogether, this suggests that preventing metastatic tumour cells from reverting to an epithelial phenotype after reaching a distant organ may reduce their ability to survive but also maintain them in a more plastic state from which they could be forced to differentiate. From a broader perspective, understanding how NC cells eventually switch off the migration program and how this arrest is linked to their ability to differentiate could give new ideas on how to prevent dissemination of tumour cells or how to treat advanced tumors that have already spread. Interestingly, cancer cells grafted back into NC migration pathways follow these routes and some are even reprogrammed to differentiate (Kasemeier-Kulesa et al., 2008; Kulesa et al., 2006). It is now clear that the different strategies of cell migration observed in cancer are reminiscent of the different migratory strategies observed during embryo development (for discussion see Mayor and Carmona-Fontaine, 2010).

These similarities suggest that spontaneous genetic modifications in tumour cells may reboot developmental programs that are to be kept off after embryogenesis. Thus, it is crucial to understand the mechanisms that trigger, control and arrest cell migration during development. The NC is the embryonic cell population that undergoes

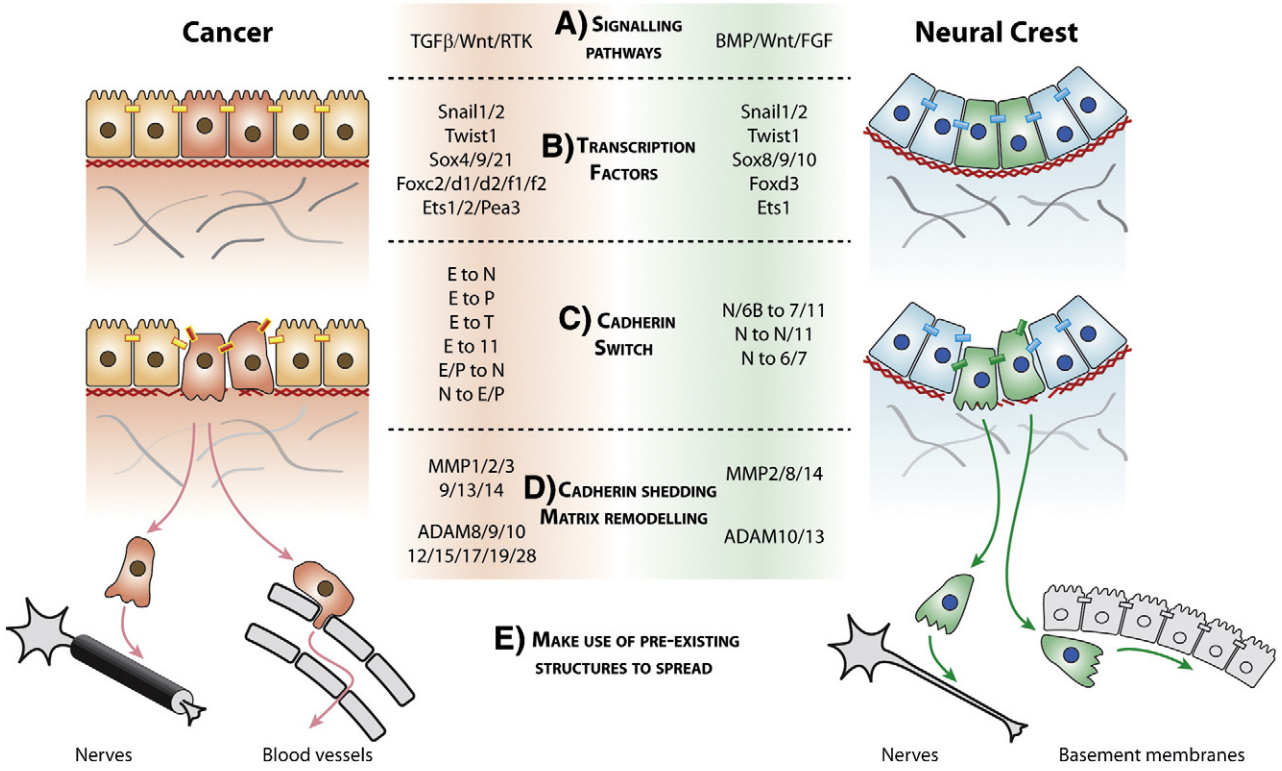

Fig. 10. Cancer metastasis and neural crest cell migration exhibit striking similarities. (A) Pre-migratory NC cells and benign tumour cells show high levels of TGFβ/BMP, Wnt and FGF/Receptor Tyrosine Kinase (RTK) signaling activity. (B) These pathways induce the expression of transcription factors of the Snail, Twist, Sox, Fox and Ets families that trigger EMT. (C) Among the changes happening during EMT, the change of cell–cell adhesion properties allows NC cells and malignant tumour cells to separate from their original tissue. (D) In addition, NC cells and tumour cells express various proteinases of the MMP and ADAM families that further contribute to the modification of cell adhesion properties by promoting remodeling of the ECM and shedding of cell surface molecules including Cadherins. (E) NC cells and tumour cells migrate in a solitary or collective fashion. Both NC cells and cancer cells make use of pre-existing structures such as nerves and blood vessels for tumour cells or nerves and the basement membrane of epithelia (such as the ectoderm and the dermomyotome) for NC cells. In addition, they both respond to external signals controlling directional migration and homing into specific tissues and organs. See main text for details and references.

the most dramatic migration. It is amenable to experimentation both in vivo and in vitro and is therefore a model of choice to address these issues.

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