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Neural crest migration: trailblazing ahead

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Abstract

Embryonic cell migration patterns are amazingly complex in the timing and spatial distribution of cells throughout the vertebrate landscape. However, advances in *in vivo* visualization, cell interrogation, and computational modeling are extracting critical features that underlie the mechanistic nature of these patterns. The focus of this review highlights recent advances in the study of the highly invasive neural crest cells and their migratory patterns during embryonic development. We discuss these advances within three major themes and include a description of computational models that have emerged to more rapidly integrate and test hypothetical mechanisms of neural crest migration. We conclude with technological advances that promise to reveal new insights and help translate results to human neural crest-related birth defects and metastatic cancer.

Introduction

One of the most striking examples of cell migration is the joyride taken by neural crest cells throughout the entire vertebrate embryo. After emerging from the dorsal neural tube in a head-to-tail order, neural crest cells begin their journey by entering diverse microenvironments rich in extracellular matrix (ECM) and other cell types. Shaped into discrete streams that stretch throughout the landscape of the developing embryo, neural crest cells travel long distances to contribute to nearly every major organ. As such, the neural crest enjoys the role of an important model system to study development and disease, including birth defects that severely affect craniofacial, cardiovascular, and autonomic nervous system function, and invasive cancers, such as melanoma and neuroblastoma, that derive from the neural crest.

In this review, we cover recent progress in the study of neural crest migration. We present new experimental results within the context of three themes that unite the complexity of embryonic cell migration patterns. We also discuss computational models of neural crest migration that have emerged to better integrate multiscale data. Together, the goal of this review is to translate and link recent findings in order to better understand the mechanistic nature of neural crest migration.

Themes of neural crest cell migration

(a) **Persistence and linearity.** Neural crest cells show prolonged, directed movement with straight trajectories that reach precise targets.

(b) **Cohesion.** Neural crest cells maintain close contact with each other during migration, but may exchange neighbors.

(c) **Plasticity and heterogeneity.** Neural crest cells display plasticity and heterogeneity to respond to changes in the local microenvironment.

Persistence and linearity

Neural crest cells show prolonged, directed movement with straight trajectories that reach precise targets

The invasive behavior of a migrating neural crest cell has fascinated developmental biologists ever since time-lapse recordings captured the trajectories of cultured cells. These *in vitro* studies, together with static analyses of cell death and evidence of neural crest exclusion

zones, led to the widely accepted idea that *in vivo* neural crest cell persistence and linearity was driven by intrinsic signals within the neural tube to control exit location and initial cell polarity. Then, population pressure drives cells away from the neural tube and local inhibitory signals restrict cells to stereotypical pathways. What has more recently excited the field is the discovery that chemotactic factors are expressed within the embryonic neural crest microenvironment and these factors attract neural crest cells, both *in vitro* and *in vivo* [1–7]. Chemotaxis, or movement in response to a chemical stimulus, thus appears to be a major component underlying neural crest cell persistence, working together with the mechanical stimulus of population pressure and cell adhesivity to the ECM scaffold. These chemotactic factors include glial cell-derived neurotrophic factor (GDNF) previously described in the gut [1], platelet-derived growth factor (PDGF) [2,3], fibroblast growth factors [4], vascular endothelial-derived growth factor (VEGF) [5], and stromal cell-derived factor 1 (SDF1) [6,7], and have significantly changed the migration paradigm.

Chemotaxis of neural crest cells: an example from the trunk

One example of neural crest cell chemotaxis is the dynamic patterning of the peripheral nervous system and, more specifically, formation of the primary sympathetic ganglia. During primary sympathetic ganglia formation, the first emerging trunk neural crest cells begin their ventral journey by following a pathway between the neural tube and somites. In the chick trunk, SDF1 becomes expressed in a graded manner along the ventro-dorsal axis [6] and its expression is initiated by signals from the dorsal aorta [7]. When ventral migrating chemokine (C-X-C motif) receptor 4 (Cxcr4) positive neural crest cells come within range of the SDF1 signal, cells home in on the dorsal aorta [6]. Ectopic sources of SDF1 placed either dorsal [7], ventral, or adjacent to the dorsal aorta [6], entice single and neighboring neural crest cells to divert from stereotypical pathways. Curiously, later emerging Cxcr4 negative neural crest cells either continue to migrate ventral to the primary sympathetic ganglia or reverse direction mid-route and migrate to contribute to the dorsal root ganglia [6,8]. Thus, trunk neural crest persistence requires cells to respond to multiple chemotactic signals that may be spatiotemporally regulated to distribute cells into distinct targets.

Chemotactic readout and cell interactions with the local microenvironment

Our understanding of how neural crest cells interpret and respond to dynamic signals and the tissue microenvironment (including chemotaxis) has advanced. For example, the actin-binding protein actin depolymerizing factor is expressed by migrating cranial neural crest cells and when knocked down via morpholino transfection leads to the reduction of Sox10 expression and shortened migratory distance [9]. The methylation cycle enzyme S-adenosylhomocysteine hydrolase also negatively affects cranial neural crest migration, indicating that cytoplasmic protein methylation is required for proper neural crest migration [10]. Lastly, the metalloproteases play a role in stimulating neural crest migration [11–12]. *In vivo* cranial neural crest cells depend on the function of the transmembrane metalloprotease ADAM13 that, through interaction with Cadherin-11, leads to extracellular fragments that stimulate cell migration [12]. In the trunk, the control of neural crest cell speed requires the inhibition of metalloproteases via reversion-inducing cysteine-rich protein containing Kazal motifs (reversion-inducing-cysteine-rich protein with Kazal [Reck]) [11].

Computational models help to explain the mechanistic nature of persistence and linearity

A recent trend in neural crest cell migration studies has been the formal construction and integration of computational models to provide a quantitative framework to incorporate ever increasing amounts of cell behavior and molecular data. From discussions between experimentalists and theoreticians, three models of neural crest migration have emerged, including: (a) frontal expansion [13]; (b) coattraction/contact inhibition of locomotion (CIL) [14]; and (c) cell-induced gradient [15]. These models, which are described in more detail below, are not necessarily mutually exclusive, but rather reflect migratory characteristics of neural crest subpopulations in different model organisms and/or different regions of the embryo.

Frontal expansion model

The frontal expansion model of neural crest migration has, at its roots, the dispersion and proliferation of enteric neural crest cells into the open spaces of the developing gut in a rostral-to-caudal invasion pattern [13]. Cells within the wavefront move in chains, colonize an open space of the gut, but are then leapfrogged by more rostral positioned cells [16]. Beautiful live imaging of the mouse intestine in which all enteric neural crest cells express a trackable photoactivatable protein now reveals that enteric neural crest cells within the wavefront (~200 μm in length) have low directionality and low caudal advance [17]. Cells more rostral (within a 200 μm long band) travel faster to continuously leapfrog the leaders and move with an unbiased random walk, suggesting that cells do not sense gut polarity [17]. How enteric neural crest cells regulate polarity so as to advance into an open space then slow down to colonize the subregion is less clear. Phosphatase and actin regulator 4 (Phactr4) has been shown to regulate integrin signaling and is required for the collective migration of enteric neural crest cells [18].

Without Phactr4, enteric neural crest cells have random protrusions and migration [18].

Interestingly, the frontal expansion leapfrog mechanism is discontinuous, such that the foregut/midgut and hindgut regions are invaded differently. At a section of the U-shaped midgut, neural crest cells behind the wavefront step out of line to cross the mesentery then move into the lead position [19]. After these trans-mesenteric neural crest cells re-integrate into the gut, they resume the frontal expansion process [19]. Thus, the identification of a unique trans-mesenteric subpopulation of cells and their diversion along the gut superhighway highlights a switch in gut invasion mechanisms. This opens an exciting avenue to pursue the ability of these cells to distinctly respond from cells in the migratory front to local microenvironmental signals.

In a similar manner, new studies of retinoic acid during vagal neural crest cell migration show that the vagal-to-enteric transition may not simply lie in terminology (neural crest cells that emerge from the vagal level of the vertebrate axis travel long distances to reach the gut entrance where they are then termed enteric neural crest). That is, cells may have distinct responses to GDNF signals depending on their position along the migratory pathway [20]. Vagal neural crest cells exposed to retinoic acid secreted from the somites display chain migration [20]. Chain directionality to the gut entrance appears to arise from the increased expression of Ret, a receptor for GDNF [20]. When these cells enter the gut and become enteric neural crest, the cells adopt the frontal expansion mechanism as described above, where GDNF signals do not drive cell polarity (with the exception of the trans-mesenteric neural crest [17]). The ECM protein, 3d, is produced and secreted by vagal neural crest cells and promotes their migration [21]. Thus, vagal and enteric neural crest cells appear to respond differently to GDNF signals in order to find the gut entrance and then populate its entire length.

Co-attraction and the CIL model

A second model of neural crest migration is the co-attraction and CIL model [14,22]. In this model, co-attraction and CIL are coordinated to maintain a critical cell density in order to achieve collective migration and respond more efficiently to external cues. Evidence for the co-attraction of neural crest cells has been nicely shown when a differential gene expression atlas of early Xenopus development led to the identification and studies of compliment fragment C3 [14]. C3, a central component of the complement pathway, is cleaved to produce C3a, a locally secreted chemical that attracts neighboring neural crest cells [14]. Co-attraction prevents the widespread dispersal of individual neural crest cells, making CIL more efficient to generate cell polarity [23]. Further evidence for CIL has involved the examination of Par3, a G protein-coupled receptor protein that appears to regulate CIL by inhibiting the Rac-GEF Trio and Trio-mediated activation of Rac1 at cell-cell contacts [24]. Inhibition of Rac1 activation at the cell-cell contacts promotes microtubule catastrophe and leads to changes in cell polarity and in the direction of migration [24]. What remains unclear is how co-attraction is coordinated to bring cells together in a way that promotes their migration in the direction of the target (since C3a is not simply secreted from the trailing edge of a lead cell), but does not cause cells to become too clustered to effectively disperse.

It has been suggested that maintaining migrating neural crest cells in a cluster is advantageous for cells to sense external cues [22,23], although there is conflicting evidence. *In vitro* data have revealed that the chemotactic response of neural crest cells requires high cell density with almost complete loss of chemotaxis when clusters are dispersed into single cells [22]. Striking movies and measurements show that the chemotactic index of cultured neural crest cells in the presence of SDF1 beads dramatically increases as a function of cell density [22]. In contrast, the *in vivo* placement of ectopic sources of the chemotactic factors VEGF [15] or SDF1 [6,7] has been shown to divert individual neural crest cells from a dense migratory stream. Future hi-resolution *in vivo* imaging should reveal whether these individual diverting cells maintain contact with each other and neighbors in the stream through long-range cellular processes [25], or whether the breakaway cells really move as solitary individual cells.

The beautiful co-attraction/CIL mechanistic work sets the stage for further studies in Xenopus and zebrafish to address how cluster migration promotes long distance travel [26]. In an exciting interplay between the cranial neural crest and placodes, data from Theveneau and colleagues have shown an SDF1-dependent coordinated collective migration, termed "chase (neural crest cells) and run (placodes)" [26]. When SDF-Morpholino was injected into the zebrafish embryo, cranial neural crest cell migration was blocked and the placodes did not move ventrally, supporting their model that placodal cells attract neural crest cells that work to push the placode [26]. What initially attracts neural crest cells to within range of the SDF1-secreting placodes, and whether all neural crest cells or just the leading edge respond to the SDF1 signal, is unclear. What is exciting about these studies is the further evidence for neural crest cell chemotaxis and the theme that neural crest migration is a dynamic process that involves a close interaction with other cell types.

Cell-induced gradient model

One of the puzzling questions to arise with neural crest cell chemotaxis is how cells move in a directed manner when the chemoattractant signal is uniformly distributed within the microenvironment rather than in a gradient. That is, with VEGF expressed uniformly within the ectoderm directly overlying the dorsolateral migratory pathway of the cranial neural crest [5], how do cells acquire and maintain direction? Experiment and computational modeling led to the development of the "cell-induced gradient model" [15]. In this model, lead neural crest cells create and respond to a cell-induced chemotactic gradient and transmit guidance information to trailing cells that use shortrange signals to move in a directional manner [15]. Tissue growth and cell consumption act to dilute the VEGF signal and neural crest cell persistence is driven by a chemotactic response to VEGF expressed within the target branchial arch tissue [15].

Whether the cell-induced gradient mechanism acts more caudally along the vertebrate axis (at the level of the cardiac neural crest) has not yet been explored. However, new evidence suggests similar homogeneous expression of neural crest chemotactic factors. That is, SDF1 has been shown to be expressed in the chick ectoderm directly overlying the migrating cardiac neural crest [27]. Chick cardiac neural crest cells express Cxcr4 but, curiously, only their invasion of the circumpharyngeal target region, and not their initial lateral migration, is strongly affected in microRNA-Cxcr4 transfected embryos [27]. This phenotype is similar to that observed in neuropilin1- small interfering RNA-treated embryos, where pre-otic neural crest cells reach the entrance but fail to invade the second branchial arch [5]. Both pre-otic and post-otic cardiac neural crest cells express Cxcr4, but not Cxcr7 during the initial phases of migration ([27]; McLennan, unpublished data), which has been implicated in binding SDF1 and establishing a gradient, as has been shown during germ cell [28] and lateral line migration [29]. Thus, similarities in the expression patterns of neural crest cell chemotactic factors VEGF and SDF1 and cell behaviors suggest both pre-otic and post-otic neural crest cells may use a cell-induced gradient mechanism to reach peripheral branchial arch and circumpharyngeal regions, respectively.

Cohesion

Neural crest cells maintain close contact with each other during migration, but may exchange neighbors

Neural crest cells travel long distances in multicellular streams, chains, or initially as a sheet with solitary individuals at the leading edge. What is intriguing is that neural crest cells appear to maintain persistent contact with one another through short- and long-range cellular processes [24]. Reducing the number of migratory neural crest cells shows that the few surviving cells travel close together and over-proliferate to compensate for missing neighbors [30]. Whether cell contact is required for the transfer of direction information between cells is unclear. However, recent work has begun to identify the mechanisms that regulate and coordinate neural crest cell adhesion during migration.

Neural crest cells remain cohesive with one another through a number of necessary modes, including tight junctions, gap junctions and cell-cell adhesion. The cadherin family of molecules has been widely studied with respect to neural crest development, and expression changes of multiple cadherins (either by down- or up-regulation) has been shown to be necessary for proper epithelial-to-mesenchymal transition and migration [31]. Specifically during migration, alphaN-catenin, cadherin7 and cadherin 11 appear to be involved in maintaining cell neighbor relationships [31–33] and the intracellular trafficking of cadherins important for neural crest migration. For example, in zebrafish embryos deficient in Rabconnectin-3a, many neural crest cells fail to migrate and misregulate expression of cadherins [34]. In addition, tight junctions are important during neural crest cell emigration to regulate the size of the premigratory domain. When the tight junction protein cingulin is perturbed, the premigratory neural crest domain is expanded and more cells enter into discrete streams [35]. Whether cingulin has a role during migration, or in the transition of Xenopus neural crest from epithelial sheet-like to individual migration, has yet to be examined. Therefore, even though migrating neural crest cells may independently regulate their cytoskeleton, cells are continuously modulating adhesivity and cell contact with neighbors.

Plasticity and heterogeneity

Neural crest cells display plasticity and heterogeneity to respond to changes in the local microenvironment

Thinking on collective cell migration has largely considered individual cells to be homogeneous. However, recent studies have shown that subpopulations of collectively migrating cells exhibit variations in cell behavior and gene expression, depending on the location within the population. These include lateral line primordium [36], cancer invasion [37], and the neural crest [13,15,38]. During enteric neural crest cell migration, multipolar and bipolar cell shapes have been identified within migrating cells [19]. Closer examination of the frontal expansion also revealed a small subset of cells, termed "superstars", responsible for producing a disproportionately large number of progeny over time [13,38]. These data support the concept that neural crest

cells display a plasticity in cell behavior and rapidly adapt to their local microenvironment.

In the head, there are at least two distinct subpopulations of chick cranial neural crest cells within a single discrete migratory stream, identified by gene expression profiles of lead and trailing cells [15]. Importantly, during migration, the spatiotemporal order of both trunk and cranial neural crest cells is largely maintained [8,39]. Therefore, cells within the invasive front are constantly exploring new territory, and it would be predicted that there would be a stable and consistent set of genes and cell behaviors associated with these cells, unless transplanted to a new position within the stream. This is indeed the case. When trailing cranial neural crest cells are transplanted into the lead in chick, cells rapidly adopt the behavior and gene expression profile of leaders [15], strengthening the idea that neural crest cell behaviors and gene expression profiles are not hard-wired but may change depending on signals within the local microenvironment.

Neural crest cell plasticity has been observed in different species and different types of neural crest cell populations. However, the level of plasticity appears to vary greatly depending on the experimental parameters, timing, species, type of neural crest used, and definition of plasticity [40]. For example, zebrafish neural crest pigment cell fate choice is plastic and dependent on levels of Forkhead box D3 (Foxd3) and microphthalmia-associated transcription factor type A (Mitfa) [41]. Also, tissue transplantation experiments in chick reveal that vagal neural crest cells exhibit a high degree of plasticity, whereas posterior vagal neural crest cells do not [42]. Chimera experiments between quail and duck also show that there are species-specific differences that are maintained (predetermination), however neural crest cells are plastic in the sense that they can compensate for loss of cell numbers [43]. Therefore, although some predetermination exists within the neural crest, it is not mutually exclusive with plasticity.

Conclusions

The present and future work needed to better understand the complexity of neural crest migration is driven by technological advances. We can now acquire three-dimensional *in vivo* time-lapse imaging sessions of fluorescently labelled neural crest cells with single-cell resolution using two-photon microscopy. Yet, light sheet illumination [44] promises to provide faster data acquisition with less phototoxicity that will allow longer duration *in vivo* imaging of multicolour-labelled neural crest cells. Analysis of time-lapse sequences will feed directly into image analysis software [45] and agent-based computational models [13–15] capable of running thousands of predictive simulations to provide more rapid feedback on mechanistic hypotheses. Advances in brighter multicolor fluorescent probes and multi-species transgenics allow for more streamlined cell tracking [46–48]. Whole transcriptome profiling will help in the identification of currently unknown factors that influence neural crest migration and are part of the neural crest gene regulatory network [49–51]. Visual confirmation of gene expression patterns may now be multiplexed using hybridization chain reaction (HCR) technology to multiplex up to five transcripts within intact tissues [52,53]. Finally, model systems to help translate the mechanisms of neural crest migration to neural crest-derived cancer metastasis hold the promise of broadening the impact of basic research [54,55]. Thus, these tools will allow us to more widely and rapidly explore the wonderful diversity of neural crest migration throughout different regions of the embryonic landscape and in different embryo model systems.

Abbreviations

CIL, contact inhibition of locomotion; ECM, extracellular matrix; FGF, fibroblast growth factor; GDNF, glial cell-derived neurotrophic factor; PDGF, platelet-derived growth factor; SDF1, stromal cell-derived factor 1; VEGF, vascular endothelial-derived growth factor.

Disclosures

The authors declare that they have no disclosures.

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References

1. Lake JI, Heuckeroth RO: **Enteric nervous system development: migration, differentiation, and disease.** *Am J Physiol Gastrointest Liver Physiol* 2013, **305:**G1-24.

2. Eberhart JK, He X, Swartz ME, Yan Y, Song H, Boling TC, Kunerth AK, Walker MB, Kimmel CB, Postlethwait JH: **MicroRNA Mirn140 modulates Pdgf signaling during palatogenesis.** *Nat Genet* 2008, **40:**290-8.

F1000Prime RECOMMENDED

3. He F, Soriano P: **A critical role for PDGFRα signaling in medial nasal process development.** *PLoS Genet* 2013, **9:**e1003851.

F1000Prime RECOMMENDED

4. Sato A, Scholl AM, Kuhn EN, Kuhn EB, Stadt HA, Decker JR, Pegram K, Hutson MR, Kirby ML: **FGF8 signaling is chemotactic for cardiac neural crest cells.** *Dev Biol* 2011, **354:**18-30.

F1000Prime RECOMMENDED

5. McLennan R, Teddy JM, Kasemeier-Kulesa JC, Romine MH, Kulesa PM: **Vascular endothelial growth factor (VEGF) regulates cranial neural crest migration in vivo.** *Dev Biol* 2010, **339:**114-25.

6. Kasemeier-Kulesa JC, McLennan R, Romine MH, Kulesa PM, Lefcort F: **CXCR4 controls ventral migration of sympathetic precursor cells.** *J Neurosci* 2010, **30:**13078-88.

F1000Prime RECOMMENDED

7. Saito D, Takase Y, Murai H, Takahashi Y: **The dorsal aorta initiates a molecular cascade that instructs sympatho-adrenal specification.** *Science* 2012, **336:**1578-81.

F1000Prime RECOMMENDED

8. Kasemeier-Kulesa JC, Kulesa PM, Lefcort F: **Imaging neural crest cell dynamics during formation of dorsal root ganglia and sympathetic ganglia.** *Development* 2005, **132:**235-45.

9. Vermillion KL, Lidberg KA, Gammill LS: **Expression of actin-binding proteins and requirement for actin-depolymerizing factor in chick neural crest cells.** *Dev Dyn* 2014, **243:**730-8.

F1000Prime RECOMMENDED

10. Vermillion KL, Lidberg KA, Gammill LS: **Cytoplasmic protein methylation is essential for neural crest migration.** *J Cell Biol* 2014, **204:**95-109.

F1000Prime RECOMMENDED

11. Prendergast A, Linbo TH, Swarts T, Ungos JM, McGraw HF, Krispin S, Weinstein BM, Raible DW: **The metalloproteinase inhibitor Reck is essential for zebrafish DRG development.** *Development* 2012, **139:**1141-52.

F1000Prime RECOMMENDED

12. Cousin H, Abbruzzese G, McCusker C, Alfandari D: **ADAM13 function is required in the 3 dimensional context of the embryo during cranial neural crest cell migration in Xenopus laevis.** *Dev Biol* 2012, **368:**335-44.

F1000Prime RECOMMENDED

13. Newgreen DF, Dufour S, Howard MJ, Landman KA: **Simple rules for a "simple" nervous system? Molecular and biomathematical approaches to enteric nervous system formation and malformation.** *Dev Biol* 2013, **382:**305-19.

14. Carmona-Fontaine C, Theveneau E, Tzekou A, Tada M, Woods M, Page KM, Parsons M, Lambris JD, Mayor R: **Complement fragment C3a controls mutual cell attraction during collective cell migration.** *Dev Cell* 2011, **21:**1026-37.

F1000Prime RECOMMENDED

15. McLennan R, Dyson L, Prather KW, Morrison JA, Baker RE, Maini PK, Kulesa PM: **Multiscale mechanisms of cell migration during development: theory and experiment.** *Development* 2012, **139:**2935-44.

F1000Prime RECOMMENDED

16. Young HM, Bergner AJ, Anderson RB, Enomoto H, Milbrandt J, Newgreen DF, Whitington PM: **Dynamics of neural crest-derived cell migration in the embryonic mouse gut.** *Dev Biol* 2004, **270:**455-73.

17. Young HM, Bergner AJ, Simpson MJ, McKeown SJ, Hao MM, Anderson CR, Enomoto H: **Colonizing while migrating: how do individual enteric neural crest cells behave?** *BMC Biol* 2014, **12:**23.

F1000Prime RECOMMENDED

18. Zhang Y, Kim T, Niswander L: **Phactr4 regulates directional migration of enteric neural crest through PP1, integrin signaling, and cofilin activity.** *Genes Dev* 2012, **26:**69-81.

F1000Prime RECOMMENDED

19. Nishiyama C, Uesaka T, Manabe T, Yonekura Y, Nagasawa T, Newgreen DF, Young HM, Enomoto H: **Trans-mesenteric neural crest cells are the principal source of the colonic enteric nervous system.** *Nat Neurosci* 2012, **15:**1211-8.

F1000Prime RECOMMENDED

20. Simkin JE, Zhang D, Rollo BN, Newgreen DF: **Retinoic acid upregulates ret and induces chain migration and population expansion in vagal neural crest cells to colonise the embryonic gut.** *PLoS ONE* 2013, **8:**e64077.

F1000Prime RECOMMENDED

21. Akbareian SE, Nagy N, Steiger CE, Mably JD, Miller SA, Hotta R, Molnar D, Goldstein AM: **Enteric neural crest-derived cells promote their migration by modifying their microenvironment through tenascin-C production.** *Dev Biol* 2013, **382:**446-56.

22. Theveneau E, Mayor R: **Integrating chemotaxis and contact-inhibition during collective cell migration: Small GTPases at work.** *Small GTPases* 2010, **1:**113-7.

23. Theveneau E, Mayor R: **Neural crest delamination and migration: from epithelium-to-mesenchyme transition to collective cell migration.** *Dev Biol* 2012, **366:**34-54.

F1000Prime RECOMMENDED

24. Moore R, Theveneau E, Pozzi S, Alexandre P, Richardson J, Merks A, Parsons M, Kashef J, Linker C, Mayor R: **Par3 controls neural crest migration by promoting microtubule catastrophe during contact inhibition of locomotion.** *Development* 2013, **140:**4763-75.

F1000Prime RECOMMENDED

25. Teddy JM, Kulesa PM: **In vivo evidence for short- and long-range cell communication in cranial neural crest cells.** *Development* 2004, **131:**6141-51.

F1000Prime RECOMMENDED

26. Theveneau E, Steventon B, Scarpa E, Garcia S, Trepat X, Streit A, Mayor R: **Chase-and-run between adjacent cell populations promotes directional collective migration.** *Nat Cell Biol* 2013, **15:**763-72.

F1000Prime RECOMMENDED

27. Escot S, Blavet C, Härtle S, Duband J, Fournier-Thibault C: **Misregulation of SDF1-CXCR4 signaling impairs early cardiac neural crest cell migration leading to conotruncal defects.** *Circ Res* 2013, **113:**505-16.

F1000Prime RECOMMENDED

28. Boldajipour B, Mahabaleshwar H, Kardash E, Reichman-Fried M, Blaser H, Minina S, Wilson D, Xu Q, Raz E: **Control of chemokine-guided cell migration by ligand sequestration.** *Cell* 2008, **132:**463-73.

F1000Prime RECOMMENDED

29. Valentin G, Haas P, Gilmour D: **The chemokine SDF1a coordinates tissue migration through the spatially restricted activation of Cxcr7 and Cxcr4b.** *Curr Biol* 2007, **17:**1026-31.

F1000Prime RECOMMENDED

30. Ridenour DA, McLennan R, Teddy JM, Semerad CL, Haug JS, Kulesa PM: **The neural crest cell cycle is related to phases of migration in the head.** *Development* 2014, **141:**1095-103.

31. McKeown SJ, Wallace AS, Anderson RB: **Expression and function of cell adhesion molecules during neural crest migration.** *Dev Biol* 2013, **373:**244-57.

32. Wu C, Hooper RM, Han K, Taneyhill LA: **Migratory neural crest cell αN-catenin impacts chick trigeminal ganglia formation.** *Dev Biol* 2014, **392:**295-307.

F1000Prime RECOMMENDED

33. Becker, Sarah FS, Mayor R, Kashef J: **Cadherin-11 mediates contact inhibition of locomotion during Xenopus neural crest cell migration.** *PLoS ONE* 2013, **8:**e85717.

F1000Prime RECOMMENDED

34. Tuttle AM, Hoffman TL, Schilling TF: **Rabconnectin-3a regulates vesicle endocytosis and canonical Wnt signaling in zebrafish neural crest migration.** *PLoS Biol* 2014, **12:**e1001852.

F1000Prime RECOMMENDED

35. Wu C, Jhingory S, Taneyhill LA: **The tight junction scaffolding protein cingulin regulates neural crest cell migration.** *Dev Dyn* 2011, **240:**2309-23.

F1000Prime RECOMMENDED

36. Xu H, Ye D, Behra M, Burgess S, Chen S, Lin F: **Gβ1 controls collective cell migration by regulating the protrusive activity of leader cells in the posterior lateral line primordium.** *Dev Biol* 2014, **385:**316-27.

37. Friedl P, Locker J, Sahai E, Segall JE: **Classifying collective cancer cell invasion.** *Nat Cell Biol* 2012, **14:**777-83.

38. Cheeseman BL, Zhang D, Binder BJ, Newgreen DF, Landman KA: **Cell lineage tracing in the developing enteric nervous system: superstars revealed by experiment and simulation.** *J R Soc Interface* 2014, **11:**20130815.

39. Kulesa PM, Teddy JM, Stark DA, Smith SE, McLennan R: **Neural crest invasion is a spatially-ordered progression into the head with higher cell proliferation at the migratory front as revealed by the photoactivatable protein, KikGR.** *Dev Biol* 2008, **316:**275-87.

F1000Prime RECOMMENDED

40. Sandell LL, Trainor PA: **Neural crest cell plasticity. size matters.** *Adv Exp Med Biol* 2006, **589:**78-95.

41. Curran K, Lister JA, Kunkel GR, Prendergast A, Parichy DM, Raible DW: **Interplay between Foxd3 and Mitf regulates cell fate plasticity in the zebrafish neural crest.** *Dev Biol* 2010, **344:**107-18.

F1000Prime RECOMMENDED

42. Kuo BR, Erickson CA: **Vagal neural crest cell migratory behavior: a transition between the cranial and trunk crest.** *Dev Dyn* 2011, **240:**2084-100.

F1000Prime RECOMMENDED

43. Fish JL, Sklar RS, Woronowicz KC, Schneider RA: **Multiple developmental mechanisms regulate species-specific jaw size.** *Development* 2014, **141:**674-84.

F1000Prime RECOMMENDED

44. Mahou P, Vermot J, Beaurepaire E, Supatto W: **Multicolor two-photon light-sheet microscopy.** *Nat Methods* 2014, **11:**600-1.

F1000Prime RECOMMENDED

45. Eliceiri KW, Berthold MR, Goldberg IG, Ibáñez L, Manjunath BS, Martone ME, Murphy RF, Peng H, Plant AL, Roysam B, Stuurman N, Stuurmann N, Swedlow JR, Tomancak P, Carpenter AE: **Biological imaging software tools.** *Nat Methods* 2012, **9:**697-710.

46. Pan YA, Livet J, Sanes JR, Lichtman JW, Schier AF: **Multicolor Brainbow imaging in zebrafish.** *Cold Spring Harb Protoc* 2011, **2011: pdb.prot5546.**

47. Sato Y, Lansford R: **Transgenesis and imaging in birds, and available transgenic reporter lines.** *Dev Growth Differ* 2013, **55:**406-21.

48. Kulesa PM, McKinney MC, McLennan R: **Developmental imaging: the avian embryo hatches to the challenge.** *Birth Defects Res C Embryo Today* 2013, **99:**121-33.

49. Hagiwara K, Obayashi T, Sakayori N, Yamanishi E, Hayashi R, Osumi N, Nakazawa T, Nishida K: **Molecular and cellular features of murine craniofacial and trunk neural crest cells as stem cell-like cells.** *PLoS ONE* 2014, **9:**e84072.

F1000Prime RECOMMENDED

50. Simões-Costa M, Tan-Cabugao J, Antoshechkin I, Sauka-Spengler T, Bronner ME: **Transcriptome analysis reveals novel players in the cranial neural crest gene regulatory network.** *Genome Res* 2014, **24:**281-90.

F1000Prime RECOMMENDED

51. Simões-Costa M, Bronner ME: **Insights into neural crest development and evolution from genomic analysis.** *Genome Res* 2013, **23:**1069-80.

F1000Prime RECOMMENDED

52. Choi, Harry MT, Chang JY, Le Trinh A, Padilla JE, Fraser SE, Pierce NA: **Programmable in situ amplification for multiplexed imaging of mRNA expression.** *Nat Biotechnol* 2010, **28:**1208-12.

F1000Prime RECOMMENDED

53. Choi Harry MT, Beck VA, Pierce NA: **Next-generation in situ hybridization chain reaction: higher gain, lower cost, greater durability.** *ACS Nano* 2014, **8:**4284-94.

F1000Prime RECOMMENDED

54. Ablain J, Zon LI: **Of fish and men: using zebrafish to fight human diseases.** *Trends Cell Biol* 2013, **23:**584-6.

55. Bailey CM, Kulesa PM: **Dynamic Interactions between Cancer Cells and the Embryonic Microenvironment Regulate Cell Invasion and Reveal EphB6 as a Metastasis Suppressor.** *Mol Cancer Res* 2014, **12:**1303-13.