Elucidating multiscale mechanisms of neural crest migration

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***Short Abstract* — The neural crest (NC) is an excellent model to study embryonic cell migration. However, it is still unclear how mechanisms are integrated in space and time to produce the migratory pattern. Here we combine an integrated modeling and experimental approach to study how the population of NC cells are coordinated to produce an ordered invasion. We present experimental data that challenges how NC cells respond to local signals and predictions from our 2D multiple agent type model. We show how repeated cylces of model construction, experimental validation and testing are vital for furthering our understanding of NC cell biology.**

***Keywords* — Neural crest, cell migration, embryogenesis, mathematical modeling, numerical simulation.**

THE neural crest (NC) is an excellent model to study embryonic cell migration (reviewed in [1,2]). NC cells emerge all along the vertebrate axis in a rostral-to-caudal manner and are driven along stereotypical migratory pathways to precise targets. Hypothetical mechanisms have emerged to explain individual NC cell behaviors and the formation of NC cell migratory streams. However, it is still unclear how these mechanisms are integrated in time and space to produce an orderly invasion program.

Here, we address two fundamental questions in NC biology: (i) how do cells interpret signals to direct their migration; and (ii) how is this linked with their migratory pattern? We combine a theoretical and experimental approach to investigate a model for the cranial NC cell migratory pattern.

Our mathematical model aims to investigate various possible scenarios for cell invasion with a view to determining experiments to distinguish between them. We idealize the cranial NC cell migratory route to lie on a two-dimensional rectangular domain. We model cells as off-lattice agents within this domain which interact with Vascular Endothelial Growth Factor (VEGF) which, in light of recent evidence [3,4], serves as a chemoattractant whose concentration is governed by a partial differential equation that describes the diffusion, uptake and production of VEGF. If space is available, NC cells every 30 minutes enter at the left boundary of the domain and move up spatial gradients in VEGF concentrations. Cells internalize the chemoattractant close to them, thus depleting VEGF in the areas that have been populated for the longest periods of time. This creates a gradient of VEGF, which may be followed to the end of the migratory route.

We find that two separate subpopulations of lead and trailing NC cells that respond differently to local microenvironmental signals are necessary. Based on this prediction we carried out molecular profiling of lead versus trailing subpopulations of NC cells, by laser capture microdissection and qPCR, which revealed striking differences of several genes that were either largely up- or down-regulated depending on NC cell position. Ablation of trailing NC cells or tissue transplantation experiments that moved NC cells from lead to trailing positions along the migratory route, or vice-versa, showed that NC cells altered their molecular profile to their new stream position. Model simulations successfully predicted aspects of the experimental results and suggest that the cranial NC cell migratory pattern is scale invariant.

Thus, by integrating mathematical modeling and computer simulation with *in vivo* imaging we have a better understanding of NC cell migration and demonstrate how repeated cycles of model construction that are simultaneously integrated with experimental validation and testing can be successful. The outcomes of this study may impact not only NC biology and mathematical biology, but also have downstream applications for the diseases that result from the mistakes in NC cell and other types of invasive cell migration, such as metastatic cancer.

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