Dynamics of leader-follower transitions in neural crest cell migration.

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Abstract

Neural crest cell migration is an important feature of vertebrate development and an emerging system for metastatic invasion. Mechanistic insight into the dynamics of intercellular and cell-microenvironmental interactions underlying this long-distance migration, however, has remained incomplete, particularly in mammalian and closely related avian model systems. We study how leading and trailing subpopulations of cells are determined in the chick cranial neural crest. These cell subtypes are thought to be induced by different microenvironmental cues and to transmit directional information between each other. We interrogate our hypotheses about the main cue, vascular endothelial growth factor (VEGF), using a combination of *in vivo*, *in vitro* and computational experiments. First we present a new, simple hypothesis for the phenotypic switching between leader and follower cell behaviour. To test the timescale of this transition, we measure gene expression of neural crest cells over time after removal of and re-exposure to VEGF. These results, in turn, are used to parametrise our model simulations. Next, we test the capacity of exogenous VEGF to change cell type and re-route migration, as well as the effect of removing endogenous VEGF from the lead and trailing subpopulations separately. In each case, we pair *in vivo* experiments with model simulations that implement and test our hypotheses for their ability to produce the observed outcomes.

Discussion and Conclusion

- Neural crest cells grown in culture have different molecular profiles to those in the embryo.
- The molecular profiles of neural crest cells in culture respond to changes in VEGF within minutes (Fig. 1-3).
- Ectopic sources of VEGF can disrupt stream migration. Trailing cells cluster, lead cells migrate onwards (Fig. 5).
- Consistent with our hypothesis and model, VEGF is not necessary for collective migration of trailing cells (Fig. 6).

→ VEGF is one of the embryonic microenvironmental signals guiding migration and driving lead neural crest cell identity.

Acknowledgements

LJS would like to thank Louise Dyson for helpful discussions and access to the code from [?] and gratefully acknowledges the U.K. Engineering and Physical Sciences Research Council for funding through a studentship at the Life Science Interface Doctoral Training Centre of the University of Oxford.

Fig. 1: Response of gene expression to VEGF

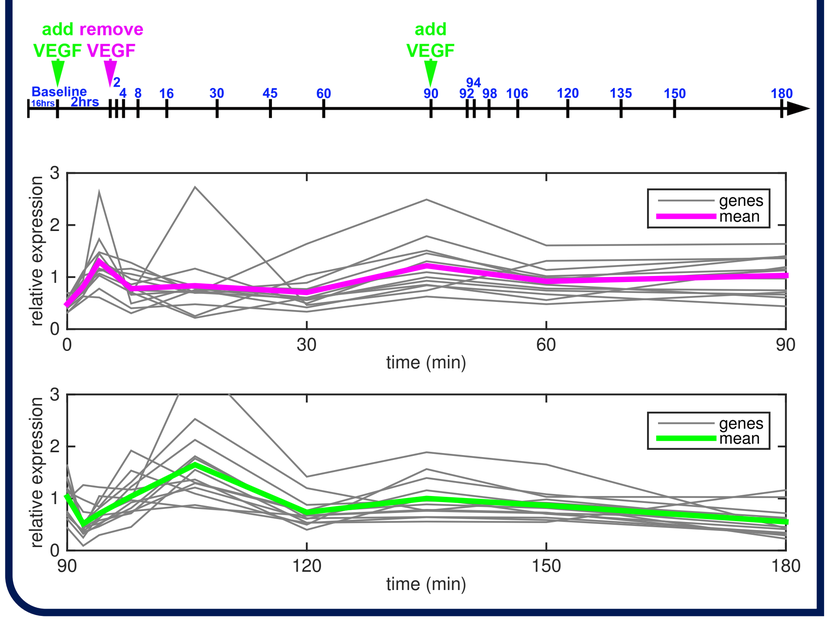


Fig. 2: Timing of first significant responses

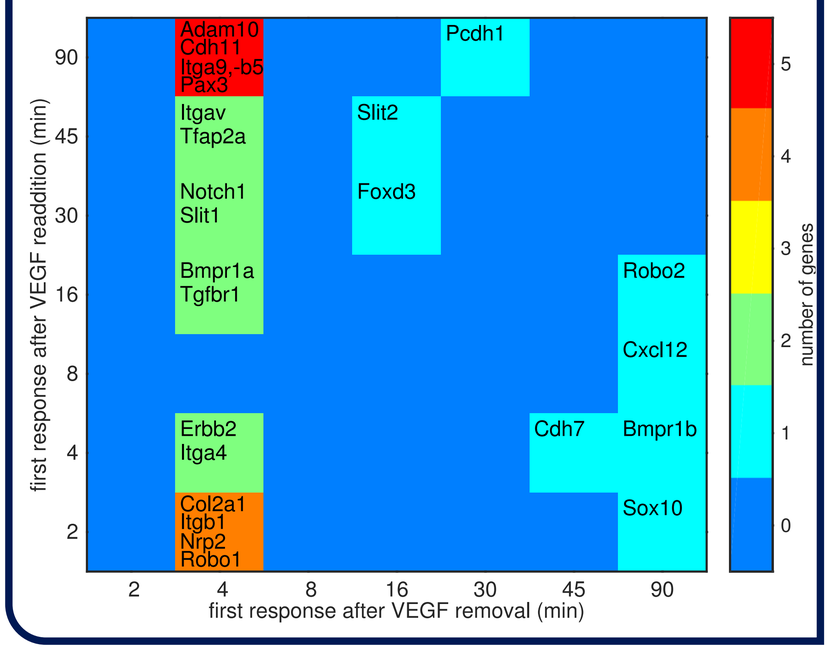


Fig. 3: Timecourse of early-response genes

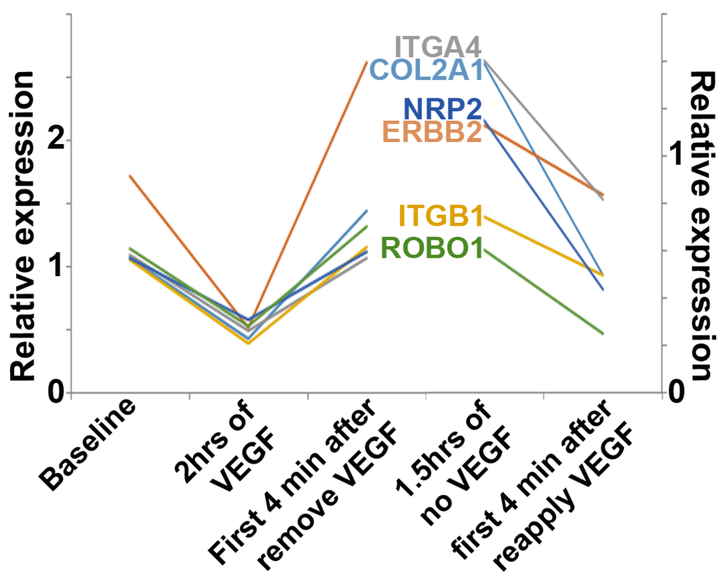


Fig. 4: "Integrate and switch" model

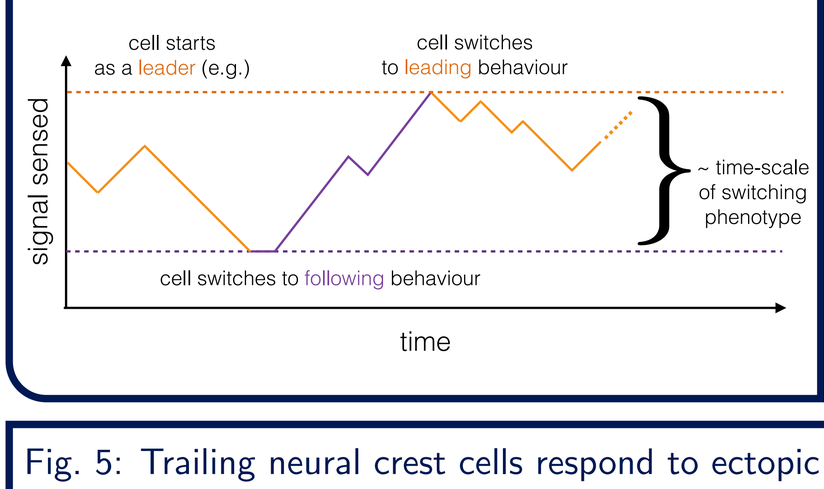


Fig. 5: Trailing neural crest cells respond to ectopic VEGF in *in vivo* and computational experiments

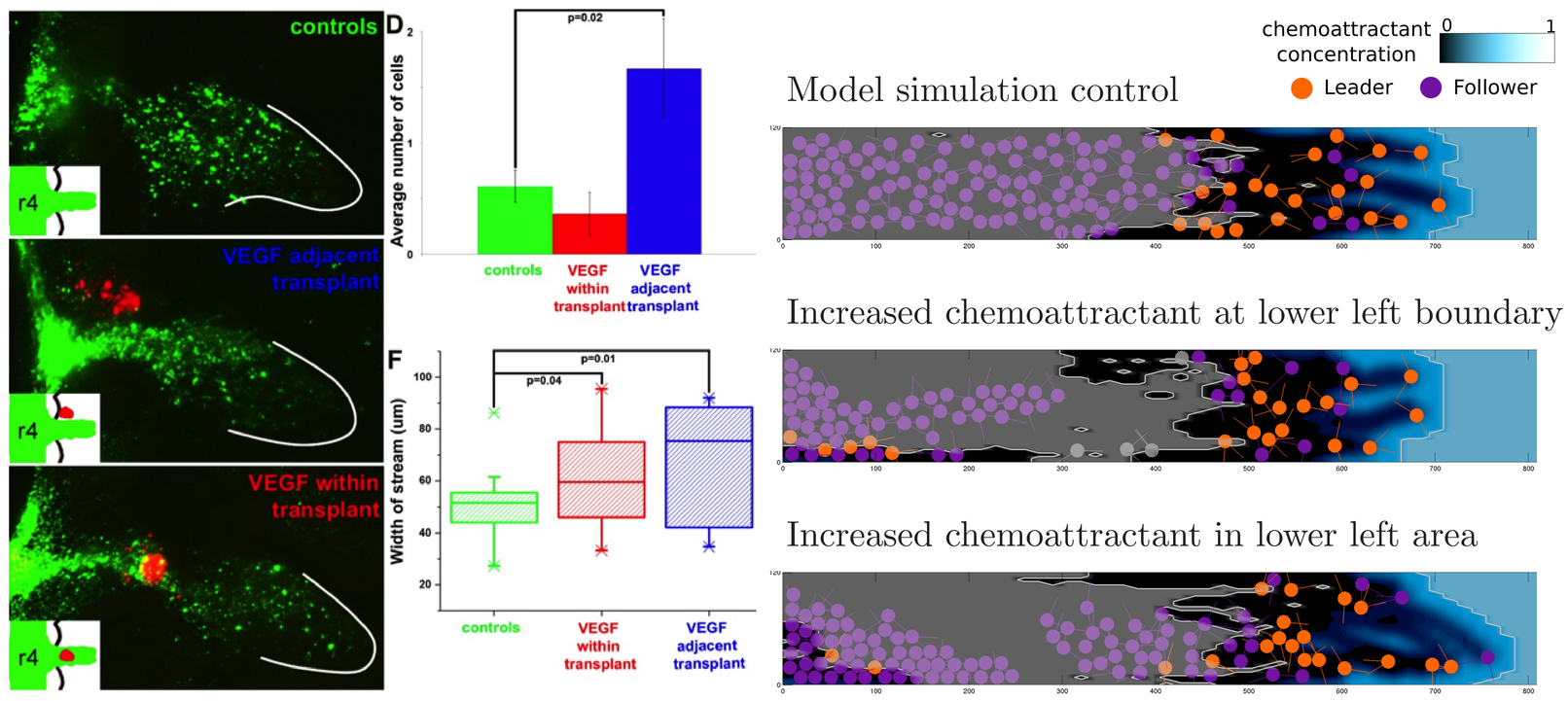
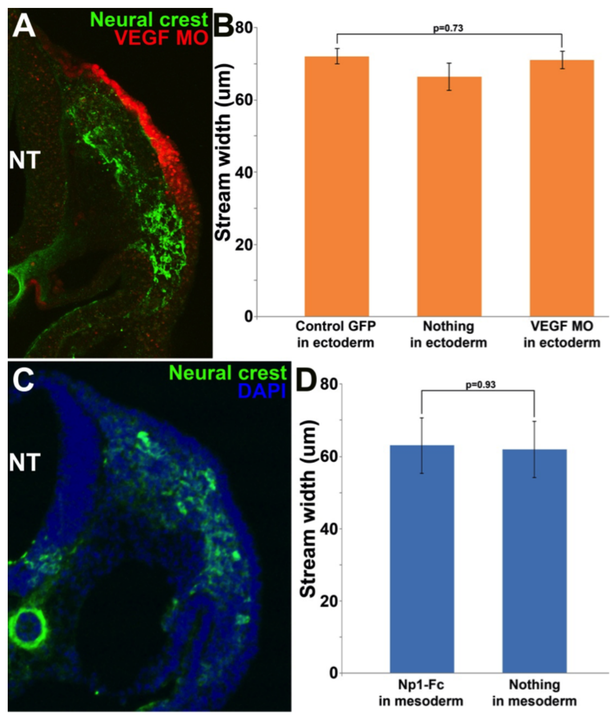


Fig. 6: Trailing cells migrate independent of VEGF



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