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GDNF and Hirschsprung Disease

How Loss of Ventral Migrating Neural Crest Can Cause a Syndrome wherein the Intestine Cannot Properly Void Solid Wastes

Glial-derived neurotrophic factor (GDNF) activates cell division, directs cell migration into the gut mesoderm, and induces neural differentiation in the enteric neural crest cells, the neural crest from the vagal and sacral regions (Mwizerwa et al. 2011). If either GDNF or Ret is deficient in mice or humans, the pup or child suffers from Hirschsprung disease, a syndrome wherein the intestine cannot properly void solid wastes. In humans, this condition is most often due to the failure of the vagal neural crest cells to complete their colonization of the hindgut, thus leaving a section of the lower intestine without the ability to undergo peristalsis. By combining experimental analysis of crest cell migration with mathematical modeling, Landman and colleagues (2007) modeled the migration of the vagal crest cells and explained the genetic deficiencies that cause Hirschsprung disease. In their model, the vagal crest cells normally do not migrate in a directed manner once they are in the anterior portion of the gut. Rather, they proliferate until all the niches in that region of the intestine are saturated, after which the migrating front moves posteriorly (Simpson et al. 2007). Meanwhile, the gut itself continues to elongate. Whether or not the colonization is complete depends on the initial number of vagal crest cells entering the anterior gut and the ratio of cell motility to gut growth. These results were not intuitively obvious just from physical observation, and the study shows the power of combining experimental and mathematical approaches to development.

Literature Cited

Landman, K. A., M. J. Simpson and D. F. Newgreen. 2007. Mathematical and experimental insights into the development of the enteric nervous system and Hirschsprung's disease. *Dev. Growth Diff.* 49: 277–286.
PubMed Link

Mwizerwa, O., P. Das, N. Nagy, S. E. Akbareian, J. D. Mably and A. M. Goldstein. 2011. Gdnf is mitogenic, neurotrophic, and chemoattractive to enteric neural crest cells in the embryonic colon. *Dev. Dyn.* 240: 1402–1411.
PubMed Link

Simpson, M. J., D. C. Zhang, M. Mariani, K. A. Landman, and D. F. Newgreen. 2007. Cell proliferation drives neural crest cell invasion of the intestine. *Dev. Biol*. 302: 553–568.
PubMed Link