Research Report: Development of the Enteric Nervous System

By Julie Albertus, M.S.

The human gut is an incredible biological structure. It has a neural network that rivals the brain in complexity: it can function independently and respond to its environment. (The Second Brain, by Michael Gershon, MD, was a best-seller that describes the wonders of the gut and the major role it plays in human well-being!) Many researchers all over the world have made it their life's work to increase our understanding of this amazing system. Some are focused on a particular gastrointestinal disease, such as Hirschsprung disease (HSCR), while others are examining general principles that are important to the gut's overall structure and function. Many of these researchers attended a meeting sponsored by the New York Academy of Medicine in New York City in March 2006. Here is an overview of just a few of the most intriguing ideas that scientists are pursuing in the field today! They can be grouped by their focus on **cells**, **signals**, or **genes**.

Cells

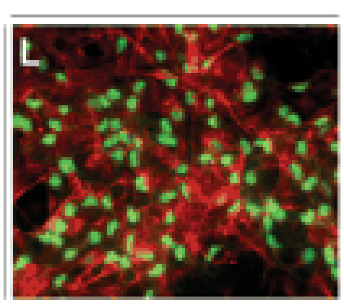
How do nerve cells in the developing embryo become an integral part of the gut? Ganglion cells—which are the cells lacking in HSCR—are derived from neural crest cells, some of the most primitive cells in an embryo. These cells must first move to the correct position, take up residence, and then differentiate into a more specialized cell type with a particular role.

Migration

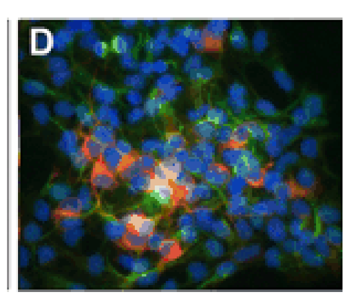
Neural crest cells must migrate through the developing embryo from the brain region to the developing gut. The cells in the lead are called the "wavefront", and they are followed by chains of cells trailing behind. Intriguingly, it seems that if a cell gets detached from a chain, it stops and goes no further. There is evidence to suggest that a particular molecule, called *L1CAM* is important in cell-to-cell interactions, allowing the cells to "stick together" and migrate as chains into the gut.[1] Interestingly, mathematical models have been developed which simulate the migration of cells into the gut, and have provided insights on migration, including the importance of the total number of cells.[2]

Stem cells

Although a long way from being useful in humans, researchers have begun experimenting with gut stem cells in animals. A group from the University of Michigan took neural crest stem cells from a rat with a genetic defect that prevented the cells from migrating to the gut. They cultured them in a dish, and then replaced them in an aganglionic rat. The transplanted cells survived, colonized the gut, and differentiated into specialized cells, effectively bypassing the migration defect![3]

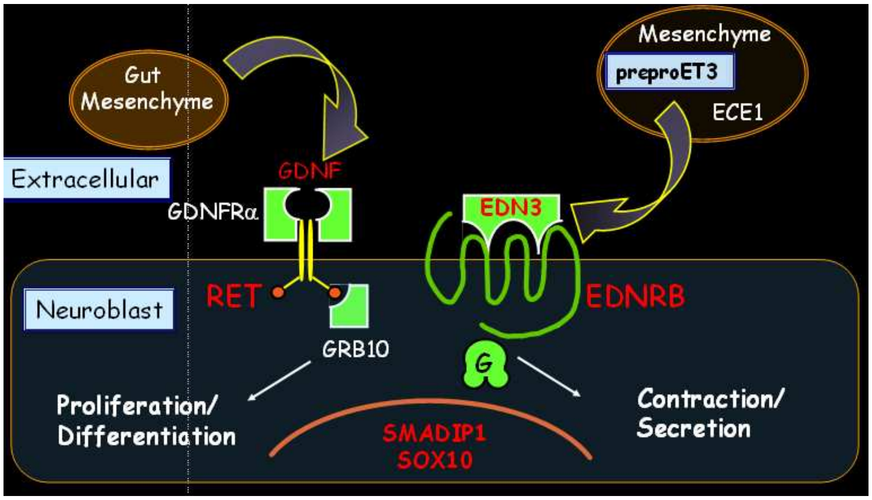


Gut cells in embryonic mice. Researchers look for expression of specific molecules.[4]



Signals

Thousands of chemical signals, interacting with each other at precise time points, are important in gut development. One signal may set off a chain of additional signals, and scientists are interested in understanding these "cascades" that eventually exert a biological effect. How do these signals direct cells in where to go, how to differentiate, and how much to grow? How do they receive and transmit signals? This is an area of active research.



Schematic of one signaling pathway involved in gut development. Taken from the Metabolic and Molecular Basis of Inherited Disease, Chap. 251 (2001).

Motility

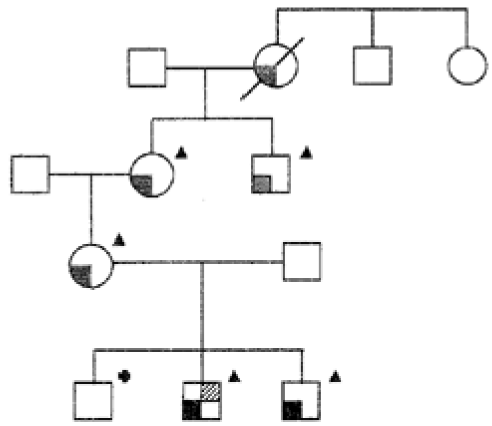
A researcher from Sweden uses frog eggs to study the biology of peristalsis—the wavelike contractions that propel materials through the gut. In the transparent embryo, they can actually see the gut's motions![5] The waves are caused by signals which initiate, propel, and inhibit contractions.

Genes

Scientists who study genetics want to understand the basis for normal and abnormal development of the gut at the most basic level: DNA. DNA is the "blueprint" for an organism—dictating physical characteristics as well as health and susceptibility to disease. Genetic researchers are trying to answer questions such as:

What genes cause HSCR?

Genes are simply functional units of DNA. It is known that there are many genes implicated in causing HSCR. Some are involved in making the chemical signals shown above, such as *RET* and *GDNF*. Some scientists have particular interest in "syndromic" forms of HSCR (aganglionosis occurring with other abnormalities, such as pigmentary abnormalities), and have described families with numerous affected individuals. Samples from some of these families have been crucial in identifying new Hirschsprung-related genes.



This is an example of a multi-generational family studied by Hirschsprung researchers.[6] (Squares represent males, and circles represent females.)

How do changes (mutations) in DNA result in disease?
Here is one example: Researchers at the National Institutes of Health who are studying a gene called *SOX10*, (which causes Waardenburg-Shah syndrome in some cases), discovered a deletion *outside* the gene that could cause the disease![7] This indicates there is another sequence in the genome that is important in regulating the *SOX10* gene. They are further exploring how this works.

Animal models
Many researchers are using animal models of intestinal aganglionosis. Interestingly, DNA sequences are similar enough between mice and humans that scientists can study mutations in these animals and apply them to humans to some extent. For example, there is a mouse strain that has aganglionosis due to defects in the *RET* gene—the main gene implicated in human HSCR. One advantage to using animals is that successive generations of mice, chicken, or zebrafish, for example, can be bred in a short time period, and scientists can see how these genetic defects are passed through generations.

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Why does scientific research matter for Hirschsprung and other diseases?
By adding to our knowledge of basic developmental processes, scientists increase our understanding of went wrong to cause the disease. This paves the way for improved diagnosis and treatment. The future is hopeful for those with gastrointestinal diseases!

**If you are interested in participating in an ongoing genetic study of Hirschsprung disease at Johns Hopkins University, please contact Julie Albertus at jalbert3@jhmi.edu or (410) 502-7541. For more information, you may also visit our website: http://www.hopkinsmedicine.org/geneticmedicine/ClinicalResources/Hirschsprung/HomeHirschsprung.html

References

[1] Anderson RB et al. *Gastroenterology:* 130(4):1221-32 (2006).
[2] D. Newgreen, paper presented at the Development of the Enteric Nervous System meeting, New York, NY, 27 March 2006, sponsored by the New York Academy of Medicine.
[3] J. Mosher, paper presented at the Development of the Enteric Nervous System meeting, New York, NY, 29 March 2006, sponsored by the New York Academy of Medicine.
[4] Bondurand N et al. *Development:* 133(10):2075-2086 (2006).
[5] M. Sundqvist, paper presented at the Development of the Enteric Nervous System meeting, New York, NY, 29 March 2006, sponsored by the New York Academy of Medicine.
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[6]Romeo et al. *J. Int. Med.*: 243(6) : 515 (1998).
[7]Antonellis A et al. *Hum Mol Genet.*: 15(2):259-71 (2006).