Neural crest cells contribute an astrocyte-like glial population to the spleen

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Neural crest cells (NCC) are multi-potent cells of ectodermal origin that colonize diverse organs, including the gastrointestinal tract to form the enteric nervous system (ENS) and hematopoietic organs (bone marrow, thymus) where they participate in lymphocyte trafficking. Recent studies have implicated the spleen as an anatomic site for integration of inflammatory signals from the intestine with efferent neural inputs. We have previously observed alterations in splenic lymphocyte subsets in animals with defective migration of NCC that model Hirschsprung's disease, leading us to hypothesize that there may be a direct cellular contribution of NCC to the spleen. Here, we demonstrate that NCC colonize the spleen during embryogenesis and persist into adulthood. Splenic NCC display markers indicating a glial lineage and are arranged anatomically adjacent to blood vessels, pericytes and nerves, suggesting an astrocyte-like phenotype. Finally, we identify similar neural-crest derived cells in both the avian and non-human primate spleen, showing evolutionary conservation of these cells.

Corresponding author Ankush Gosain, MD, PhD, discussed the inspiration for and findings of this study:

1. What was your inspiration for this study?

My lab has been working to understand the role of the body's immune system in the pathogenesis of Hirschsprung-associated enterocolitis, which is a potentially life-threatening complication of Hirschsprung disease.

We previously found that levels of a specific type of immune cell, the mature B lymphocyte, are abnormally low in the intestine and abnormally high in the spleen of Hirschsprungs disease animals. We have developed a mouse in which the neural crest cells, which are the cells that normally make the enteric nervous system and are altered in Hirschsprung disease, fluoresce under a microscope. Using this mouse, we saw that some neural crest cells enter the spleen during development.

2. Did you discover anything during your research that was surprising?

Finding neural crest cells in the spleen was surprising - nobody has ever described that before. The next obvious questions became how do they get there, when do they get there, and what could they be doing? We did a detailed study of these cells during embryonic development and after the animals are born to answer these questions. We found that the cells enter the spleen before the mice are born, late in development. As they are entering the spleen, they differentiate and become glial cells that look like astrocytes. In the brain, astrocytes are the cells that control communication between the circulation and the neurons of the central nervous system. We think, based on what the cells in the spleen look like and how they are positioned, that they may be doing the same thing in the spleen.

3. Why do these findings matter for kids with Hirschsprung disease?

It is too early to say what the direct relevance to kids with Hirschsprung disease is. We are continuing our work with these cells to better understand their function. We hypothesize that they help control how the spleen responds to infection. By sitting between the blood vessels and the neurons in the spleen, they are perfectly positioned to communicate between these two systems. If we are right, this will be important not just for patients with Hirschsprung disease, but any patient with an infection.

More information: Amanda J. Barlow-Anacker et al, Neural Crest Cells Contribute an Astrocyte-like Glial Population to the Spleen, *Scientific Reports* (2017). DOI: 10.1038/srep45645

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