Neural crest cell migration in Hirschsprung disease

13 October 2020

Ankush Gosain, MD, Ph.D., of Le Bonheur Children's Hospital and the University of Tennessee Health Science Center has focused his research on determining the mechanisms underlying abnormal development of the enteric nervous system in Hirschsprung disease. Gosain recently published a new study in *The FASEB Journal* delineating interactions between migrating neural crest cells and the extracellular matrix in a model of Hirschsprung disease using a variety of in vitro and in vivo approaches.

Neurons in the wall of the gastrointestinal tract comprise the enteric nervous system, which controls gut motility, digestion, secretion and absorption. During development, neural crest cells, the precursors of neurons in the enteric nervous system, migrate throughout the digestive tract to provide innervation. However, in Hirschsprung disease, neural crest cells fail to migrate into the distal colon, resulting in a lack of innervation in this region. This lack of innervation is a common cause of neonatal bowel obstruction, which can progress to bowel distension, Hirschsprung-associated enterocolitis and death.

Gosain and colleagues specifically focused on abnormalities in laminin expression as laminin is a potential regulator of interactions between migrating neural crest cells and the extracellular matrix in the developing enteric nervous system. The investigators used a mouse model of Hirschsprung disease, the endothelin receptor B knockout mouse, to tease out specific changes in laminin expression.

In the knockout mice, the gene encoding laminin ?1 was upregulated more than two fold. By contrast, the receptor for laminin ?1, LAMR, showed decreased expression in samples from knockout mice and human patients with Hirschsprung disease. Application of exogenous laminin-111 suppressed NCC migration in an organ culture model, whereas YIGSR, a laminin ?1 analog, promoted NCC migration. YIGSR also upregulated expression of LAMR and enhanced NCC migration in midgut slice culture. When LAMR expression was silenced, the beneficial effect of YIGSR was abolished. Furthermore, YIGSR application resulted in colonization of the distal colon in 80% of ex vivo organ cultures from endothelin receptor B knockout mice.

These experiments indicate alterations in LAMR contribute to neural crest cell migration failure in enteric nervous system development. The investigators think YIGSR maysselectively enhance neural crest cell migration through LAMR with LAMR bindingsincreasing LAMR expression and preferentially promoting migration. These results addsto the current body of literature showing interactions between neural crest cells and the extracellular matrix are involved in enteric nervous system development with the extracellular matrix representing a potential target for intervention in Hirschsprung disease.

More information: Ming Fu et al, 37/67?laminin receptor facilitates neural crest cell migration during enteric nervous system development, *The FASEB Journal* (2020). DOI: 10.1096/fj.202000699R

Provided by Le Bonheur Children's Hospital