THE HARTWELL FOUNDATION

2022 Individual Biomedical Research Award

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Targeting Mechanosensitive Signaling Pathways to Modulate Gastroschisis-Related Intestinal Inflammation and Dysmotility

Gastroschisis is a complex birth defect that occurs in 1 out of every 2,000 live births, with the incidence doubling in the United States over the last two decades. It is an abdominal wall defect that occurs during fetal development, characterized by hallmark inflammation marked by the presence of proinflammatory mediators, macrophage infiltration and early T-cell activation in the fetal blood and intestines, as well as the amniotic fluid that surrounds the fetus. The herniation of the inflamed intestines into the amniotic fluid cause them to swell and shorten, contributing to severe gut dysmotility and fetal growth failure. The inflammation contributes to problems with normal bowel function after birth that can last months and requires some babies to have part of their intestines removed. With anatomic corrective surgical repair at birth most babies born with gastroschisis survive, although they will endure increased risk of profound and long-lasting morbidities, including increased risk of sepsis, necrotizing enterocolitis, short bowel syndrome, intestinal failure, feeding difficulties, and failure to thrive. Previous efforts to understand the etiology of the birth defect were focused on decreasing inflammatory mediators found in the fetal amniotic fluid but have failed to show any translatable or clinical benefit. Recent evidence has emerged, however, that mechanical stimuli such as pressure, stretch and shear stress from fluid turbulence are responsible for activating inflammatory responses in several disease states, most notably Crohn's bowel disease. Effectively, changes in the surface tension of cell membranes can open a mechanosensitive ion channel (Piezo1) that allows positively charged ions like calcium to enter the cell, triggering a series of biochemical reactions responsible for the cell's behavior. In this regard, I recently discovered that, in the smooth muscle cells of the mouse small bowel, Piezo1 is required for modulating contractile strength, rhythmicity and maintaining cell types needed to promote motility. My working hypothesis is that the Piezo1 mechanotransducer may be the missing link in understanding gastroschisis-related morbidities and that Piezo1-mediated signaling pathways become inappropriately and persistently activated, subsequently triggering inflammation. Using human specimens and a well-established fetal gastroschisis lamb model, I will use traditional molecular methods with single-cell spatial transcriptomics to show that dysregulation of Piezo1 is the critical step in the inflammatory cascade that persists and drives the damage seen in gastroschisis; and that a pharmaceutical strategy to target Piezo1 will mitigate gastroschisis-related intestinal inflammation and dysmotility. If I am successful, a minimally invasive therapeutic strategy to mitigate the detrimental morbidities associated with gastroschisis will be possible, improving the quality of life of children affected by this birth defect.