THE HARTWELL FOUNDATION

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Harnessing Gut Bacteria to Reduce the Risk of Autism in Infants Exposed to Maternal Antidepressants

Autism spectrum disorder (ASD) is a highly prevalent syndrome, affecting as many as 1 in 44 children, often leaving them with severe disabilities and lifelong restrictions. Further, there is a reported 60% increase in the risk of ASD in the infants of women who took antidepressants during pregnancy or nursing. Recent studies support a critical role for gut bacteria in driving the manifestation of ASD. However, it is unknown how gut bacteria contribute to the onset of ASD in children and the mechanistic link between the gut microbiome and immune cell development and neurodevelopment in early life remains poorly understood. The gut microbiome in infants is vastly different from that in adults due to dietary changes and maturation of the gut microenvironment. The neonatal gut metabolome, largely shaped by metabolites derived from gut bacteria, has not been well characterized. To address this limitation, I have recently compared >500 metabolites in the small intestines of neonatal and adult mice using a high-throughput metabolomics approach. Importantly, I found that most metabolites at significantly higher levels in neonates were neurotransmitters, including serotonin, a neurotransmitter critical in the regulation of gut motility, mood stabilization, and blood clotting. I demonstrated that gut bacteria drive serotonin generation in the neonatal intestine by inhibiting the expression of monoamine oxidase A (MAOA), an enzyme that breaks down serotonin. The effect would maximize serotonin availability but may predispose infants to serotonin toxicity. High levels of serotonin are consistently detected in stool specimens of infants that had been exposed to maternal antidepressants and increased blood serotonin has been commonly observed in children with ASD. In addition, I found that serotonin reduces the expression of a critical gene that is an important regulator of circadian rhythm, which when irregular has been linked to ASD. Moreover, my observations suggest that following exposure to maternal antidepressants, the intrinsically low level of MAOA in the neonatal intestine increases the likelihood of excessive intestinal and blood serotonin in infants. Based on this information, I hypothesize that given the reduced levels of MAOA in infants, an increase in intestinal serotonin leads to a rapid increase in blood serotonin that signals the brain to increase inflammation in the gut, which increases the risk of developing ASD. I propose to determine how the unique mechanism of serotonin biosynthesis in the infant intestine may contribute to increased blood serotonin and risk of ASD in infants exposed to maternal antidepressants. I will also identify the gut bacteria that can upregulate MAOA to reverse the adverse effects of maternal antidepressants on infants. If I am successful, clinical translation of an effective intervention to reduce the risk of developing ASD in infants exposed to maternal antidepressants will relieve affected children and their families of the lifelong effects of this disorder.