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2019

Azhari, A., Azizan, F., & Esposito, G. (2019). Beyond a gut feeling : how the immune system impacts the effect of gut microbiota in neurodevelopment. *Behavioral and Brain Sciences*, 42, e64-. doi:10.1017/S0140525X18002790

<https://hdl.handle.net/10356/107503>

<https://doi.org/10.1017/S0140525X18002790>

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Beyond a gut feeling: How the immune system impacts the effect of gut microbiota in neurodevelopment

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Abstract: Hooks et al. posit that gastrointestinal microbes alter the end state of development indirectly. Here, we present the immune system as the link that facilitates communication between the gut and the brain. Illustrating the case of autism spectrum disorder (ASD), we explicate the role of the immune system in responding to microbial dysbiosis by inducing an inflammatory state that affects neurodevelopment. We propose two models: directly, within the infant, and indirectly, via maternal and infant systems.

The gut microbiota has been recurrently reported to influence developmental outcomes (e.g., Finegold et al. 2002; Kang et al. 2013). Hooks et al. proposed that the mere presence of microbes in the gut triggers a response in the developing organism that results in an altered end state of development, rather than the microbes being a direct causative agent. Although we concur with this

point, it is important to further address it in relation to the immune system and how pivotal it is as an intermediary system that affects neurodevelopment (Fig. 1). To illustrate our point, we present the case of autism spectrum disorder (ASD), a neurodevelopmental condition that features restricted behaviors and deficits in social communication (American Psychiatric Association 2013). The comorbidity of

Figure 1. Schematic diagram illustrating theoretical models of direct (gut_{infant}-immune_{infant}-brain_{infant}) and indirect (immune_{maternal}-brain_{infant}) mechanisms underlying autism spectrum disorder (ASD). The direct model features atypicality in the infant's gastrointestinal microbiota, leading to system-wide and neuroinflammation in the infant. The indirect model 1 features dysregulated maternal gastrointestinal microbiota, instigating maternal immune activation (MIA) and subsequent neuroinflammation in the infant. Neuroinflammation stemming from either of the two mechanisms will compromise neurodevelopment and induce the emergence of autistic-like traits.

ASD and gastrointestinal disorders has been often reported (e.g., Ashwood & Wakefield 2006; Torrente et al. 2002). In our recent review, we showed that the risk of ASD increases with respect to the inflammatory state, rather than to the presence of a specific species of microbe, underscoring how system-wide changes in inflammatory profiles may direct neurodevelopmental trajectories (Azhari et al. 2018). Indeed, the response to gut microbiota that the organism launches is primarily composed of signals from immuno-inflammation pathways, allowing for a relay between the gut and the central nervous system (CNS) (Carabotti et al. 2015; Erny et al. 2015). This gut-immune-brain communication can be traced to several main points of contact across the systems, primarily facilitated by signaling immune molecules. The gastrointestinal microbiota has significant influence over the profile of certain circulating pro-inflammatory cytokines, chemokines, and growth factors, such as IFN- γ (interferon- γ), IL-17 (interleukin-17), IL-6 (interleukin-6), and TNF- α (tumor necrosis factor- α) (e.g., El-Ansary & Al-Ayadhi 2014). The link between autism and immune dysfunction has been asserted by findings of atypical upregulation of these cytokines in persons with autism (e.g., Li et al. 2009; Khakzad et al. 2012). Pro-inflammatory cytokines function as signaling molecules and have the capacity to communicate with the CNS, serving as a bridge between the gut microbiota and the brain. Indeed, post-mortem studies on brain tissues obtained from deceased persons with autism showed the

presence of enhanced neuroinflammation in several brain regions, including the cerebral cortex, white matter, and cerebellum (e.g., Vargas et al. 2004). Pro-inflammatory molecules responsible for this have been postulated to impede brain development indirectly, through non-neural cells. In individuals with ASD, a type of resident non-neural cell that has been found to be activated at atypical levels constitutes the microglia (e.g., Tetreault et al. 2012). Although moderate activation of the microglia in response to injury or infection in the CNS is protective, chronic microglial activation compromises brain development in one of two ways. First, abnormally activated microglia overproduce pro-inflammatory cytokines, which contributes to damage in synaptic networks and neuronal cell death (Rodriguez & Kern 2011). Second, chronically activated microglia are responsible for elevated occurrences of phagocytosis and excessive removal of neuronal debris, leading to impaired neural development (Takano 2015). Dysfunctional microglia are no longer sensitive to external immune signals either, which leads to a perpetuation of dysregulated phagocytosis (Fernández de Cossío et al. 2017). At present, accumulating evidence drives at one possible hypothesis: In autistic persons, elevated levels of pro-inflammatory cytokines may stem from the instigation of the gut microbiota onto the immune system; these immune signals contribute to neuroinflammation that ultimately hinders neurodevelopment. This theory posits a gut_{infant}-immune_{infant}-

brain_{infant} model, where biological pathways from the gut microbiota to the eventual emergence of the autistic phenotype occur within an individual. Although this hypothesis is intriguing, at present, researchers have yet to elucidate a causal pathway that proves that the dysregulation of pro-inflammatory cytokines attributable to dysbiosis of the gut microbiota is the same immune phenomenon that leads to chronically activated microglial cells in the brain of ASD individuals.

As neurodevelopment begins early in the course of fetal maturation, it is important that we address the mechanism at the prenatal phase too. Hooks et al. refuted the postulation of the gut microbiota exerting any neurodevelopmental impact given that the in utero environment is sterile. Although the notion of in utero sterility may be true, the immune system of the mother, however, could still impact the fetus during gestation. We posit that the state of generalized inflammation in the pregnant mother, maternal immune activation (MIA), potentially alters neurodevelopment in infants (e.g., Gilmore et al. 2005). This theory has largely been supported by animal studies, such as that conducted by Kim et al. (2017). In this mice study, the authors showed that specific maternal gut microbes are associated with an increase in pro-inflammatory IL-17 in the mother, along with the appearance of autistic behaviors in the offspring. A study on ASD patients showed that TNF- α , potentially secreted by liver cells in the presence of gut lipopolysaccharides (LPS), creates a peripheral inflammation that results in microglia activation in the

brain (e.g., Breese et al. 1994; Qin et al. 2007). As opposed to the first model, this second model presents an indirect immune_{maternal}-brain_{infant} pathway that involves cross-talk between the immune system of the mother and the CNS of the infant.

In conclusion, we have presented the case of ASD as a neurodevelopmental condition involving both the gut microbiota and the immune system. We have also proposed two theoretical models that the field should consider (Azhari et al. 2018). The first model features direct gut-immune-brain association within the individual at the postnatal phase, whereas the second model is an indirect model implicating both maternal and infant systems in the prenatal phase. These theoretical models may sprout experimental paradigms that allow for existing postulations to be tested and, in doing so, uncover causal pathways from the gut to the immune system and, ultimately, to the brain.

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