ALZHEIMER'S
A THERAPEUTIC DISCOVERY

MATERNAL MICROBIOTA
EFFECTS ON FETAL BRAIN DEVELOPMENT

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Alzheimer's disease (AD), a neurodegenerative disorder commonly characterized by a progressive impairment of memory and other cognitive abilities, is responsible for 60-80% of all dementia cases. AD is caused by excessive β-Amyloid (βA) deposits that form harmful plaque buildup around the brain and disrupt neural cell functions. Symptoms gradually increase in severity, beginning with minor cognitive impairment and escalating to confusion, behavioral changes, difficulty speaking or moving, and death.[1] Despite affecting over 24.2 million individuals worldwide, AD has no direct cure and treatments only aim to mitigate damage for as long as possible.[2] Most medications for AD perform two functions: they inhibit acetylcholinesterase from breaking down acetylcholine, the neurotransmitter responsible for nerve impulse transmission, and they reduce βA deposits in the brain. As a result, these therapies improve cognitive function, delaying symptoms temporarily.[3]

While traditional therapeutics focus primarily on amyloid plaques or neurofibrillary tangles, both of which involve βA deposits, one study by Price et al. has argued that that the discovery of AD involving neuroinflammation and lipid metabolism can lead to the development of novel therapeutics. Experiments in murine models have demonstrated that both the homozygous and heterozygous mutations can reduce the effectiveness of the triggering receptor expressed on myeloid cell-2 (TREM2), a lipoprotein-binding receptor. Activation of TREM2 leads to a subsequent activation of microglia, the primary innate immune cell in the central nervous system, causing them to play an active role in the degradation of βA deposits.[4] This can significantly increase the risk and severity of AD. Direct cranial injection of AL002a, a TREM2-activating murine IgG1 antibody, was also correlated with reduced βA deposition by upwards of 40%. As such, researchers could potentially develop a treatment that does not directly target the βA peptide. Overall, they hypothesize that direct targeting and promotion of TREM2 function may lead to a new and potent therapeutic response to AD.[5]

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The microbiota comprises trillions of bacteria, archaea, viruses and eukaryotic microbes that reside within and on the body. These resident microorganisms impact health and support many bodily functions throughout life, such as protecting us from pathogens, training our immune system, and assisting in metabolism.[1] Maternal challenges, including immune system activation and psychosocial stress, are known to lead to neurobehavioural abnormalities in mice offspring.[2,3] Previous research has shown that microbiota can mediate the impact of these environmental stressors to ensure proper fetal development. However, little is currently known about the mechanism by which this occurs, nor is it clear whether the microbiome has an influence on the offspring neonatally or postnatally.[3,4]

Recent research by Vuong et al. has found that certain maternal gut bacteria create metabolic byproducts that can influence embryonic brain development. Embryos of pregnant mice, that were either germ-free or had their microbiota depleted by antibiotics, were experimentally shown to have different brain structures from those of embryos of mothers with healthy microbiota.[5] In particular, embryos of germ-free mothers had thinner axon bundles and shorter, smaller axons between the cortex and thalamus, which is responsible for processing and relaying information in the brain.[6]

Upon examining the adult offspring of microbiota-deficient mothers, Vuong and colleagues found that the mice had abnormal responses to heat, sound, and pressure, indicating that sensory pathways were predominantly affected.[5] Furthermore, maternal gut microbes (the *Clostridium* genus of bacteria, in particular) affected the levels of metabolites in maternal blood and embryonic brain tissue, suggesting that interactions between the microbiome and nervous system began prenatally.[5] These findings contribute to the growing amount of research on the mechanism underlying the impact of the maternal microbiome on the developing brain. Moreover, understanding how metabolites reach the fetus might help identify potential pathways for developing future clinical interventions.

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RACIAL BIAS IN MEDICAL EDUCATION

MAKING IMPORTANT CHANGES

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A recent study from the Mayo College of Medicine found that experiences in medical school, such as formal curriculum training, play a significant role in shaping implicit biases in students.[1] Implicit biases entail the attitudes or stereotypes that impact actions and beliefs unconsciously, which may affect the medical curriculum.[2] One of the implicit biases that has been particularly well-examined over the past two decades is race, with numerous studies emphasizing the need to integrate culturally-considerate educational activities and information into the current healthcare system, along with cultural competence training to improve interpersonal quality of care. Although a majority of these studies have focused on the implicit racial bias against African Americans, it is also applicable to other ethnic minorities.[1,3]

There have been advancements in medical education that have begun to take greater consideration toward the implicit biases in teaching medicine. As mortality rates among African Americans have been shown to be higher in cases of skin cancer, often due to late diagnosis, the need for more diversity in medical reference texts has gained recognition.[4,5] Malone Mukwende, a third year medical student at the University of London, published a book in 2020 to help health professionals distinguish differences in skin conditions between Caucasian and African American individuals.[6] Additionally, rosacea, a common skin condition that causes redness, presents differently in African Americans and may be overlooked by medical professionals.[7,8] To provide a more comprehensive source of education about such skin conditions, Diya Ayodele, an aesthetician, founded the Black Skin Directory in 2018. This resource uses both de-identified images from African American patients with skin conditions such as rosacea, and descriptions of signs and symptoms, to provide a more holistic understanding of these diseases on a different skin pigment.[9] While racism still remains to be a significant societal issue, initiatives such as these are steps forward in the pursuit of equitable healthcare.

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MICROGLIA

MORE THAN JUST AN IMMUNE CELL

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The circuitry of the central nervous system (CNS) can be summarized as a system of excitatory and inhibitory signals working collectively to facilitate bodily function. Signalling occurs through the release of various neurotransmitters, whose subsequent binding to target receptors alters the target neuron's membrane potential, making it predisposed to firing a subsequent action potential.[1] While these processes are primarily attributed to neurons, there is growing evidence of the involvement of other cell types in signalling. Among these are microglia, which are the resident macrophages of the CNS responsible for active immune defense, "pruning" of neuronal synapses, and reduction of plaque deposits.[2] Despite some evidence suggesting that microglia protect neurons from overactivity with an inhibitory function of sorts, the particular mechanism remains unclear.[3]

A recent study by Badimon et al. provides evidence for one possible mechanism of microglial action.[4] Removal of microglia in murine models was shown to both increase the excitability of neurons and decrease the level of adenosine, an inhibitory neurotransmitter. This suggests that release of adenosine could be the mechanism through which inhibition occurs.[4,5] Furthermore, adenosine triphosphate (ATP) was also found to be the origin of this pathway and is released upon neuronal activation. Released ATP is converted into adenosine diphosphate (ADP), which attracts microglia to neuronal synapses prior to being converted into adenosine by microglial surface enzymes.[4] Additionally, the proximity of microglia to the synapse in this process suggests inhibition to be a localized effect impacting only grey matter, where most synapses are found.[4] These findings once again challenge the established neuron-centric dogma of neuronal signalling, adding microglia to a growing list of cell types that play a role in neural signalling.[6] More importantly, the ability of microglia to synthesize adenosine from ATP precursors presents a new target for treatments of a range of diseases where neural hyperactivity is a key component, such as epilepsy.

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