CALIFORNIA STATE SCIENCE FAIR
2012 PROJECT SUMMARY

Name(s)

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Project Number

S0532

Project Title

Exploring Neural-Immune Synergy: TNF Inhibition Protects Against Maternal Illness Induced Neuronal Dysfunction in Autism

Abstract

Objectives/Goals

Intrigued by structural parallels between the neuronal synapse and immunological cell-cell junction, I first decided to explore whether the inhibitory neurotransmitter GABA could function at the "immunological synapse" to regulate the response to infection. Second, as maternally inherited GABAR mutations and maternal infection are the most common factors contributing to autism spectrum disorders (ASD), and autistics often experience immunological dysfunction, I theorized that a neural-immune interaction, analogous to the interaction in vitro, could play a major role in ASD. I thus aimed to characterize the long term impact of maternal infection on GABAergic interneurons in the brain. The third aim was to identify a preventative strategy against maternal infection induced ASD.

Methods/Materials

I treated RAW 264.7 macrophages with LPS, an immune stimulant, and muscimol (GABA agonist) or bicuculline (antagonist). ELISA and Griess tests assessed production of hypoxia inducible factor, the cytokines TNF-a and IL-6, and nitric oxide. To characterize long term impacts of maternal infection on the offspring and determine a preventative measure, I performed immunohistochemistry, microscopy, and image analysis using ImageJ on brain tissue of WT and TNFR1 knockout mice exposed to maternal infection.

Results

Remarkably, inhibition of GABAergic signaling by bicuculline increased cytokine and nitric oxide production; heightened GABAergic signaling inhibited inflammation and hypoxia. Immunohistochemistry identified three interneuron populations impacted in the adult hippocampus and cortex. Multiple linear regression analysis revealed a novel relationship between infection and autistic like behavioral impairment, identifying a key role of parvalbumin interneurons in modulating behavior. In a novel result, TNFR1 knockout restored cortical interneuron density to within 4.2% of normal levels.

Conclusions/Discussion

While previous studies have identified GABA receptors in immune cells, this study is the first to demonstrate the function and extent of GABAergic signaling in immune cells, in roles as diverse as regulation of hypoxia and nitric oxide, both of which are key cellular messengers. This study has also identified critical therapeutic targets which correlate with autistic like behavior. TNFR1 knockout mediated protection against interneuron loss indicates the viability of TNF inhibition to prevent ASD post-infection.

Summary Statement

I identified a novel source of neural-immune synergy in macrophages and applied my findings to characterize and develop a preventative strategy against maternal infection induced interneuron dysfunction, a leading cause of autism.

Help Received

Used lab equipment at the Palmer Lab and HTBC of Stanford University. Palmer Lab provided behavioral data for analysis. ADRF funded cell culture studies. BABEC, Invitrogen, NanoEnTek, Cayman Chemical, Bio-Rad, Cell Signaling Technology, Jr Scientific, eBioscience, and R&D donated reagents.