The Impact of IL-6 on the interplay between neurons and astrocytes in Rett Syndrome

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Scientific Abstract:

The development of autistic features, such as social withdrawal and loss of eye contact, characterize the behavioral and motor regression of Rett Syndrome (RTT). RTT patients have difficulty walking or lose the ability entirely and display repetitive hand movements. That the behavioral and motor features of RTT appear around the same time as Autism Spectrum Disorder (ASD) patients suggests a common underlying biological process. Another important link between ASD and RTT is an imbalance in cytokine signaling. Cytokines are important signaling molecules responsible for cell maturation and inflammation. Interleukin-6 (IL-6) is mainly a pro-inflammatory cytokine present during trauma or infection. IL-6 has been widely associated with ASD; a single injection of IL-6 in a pregnant mouse will produce offspring with autistic features. Furthermore, IL-6 has been linked to alterations in ASD patients' brains, affecting neural cell adhesion, migration, and synapse formation. Using a human iPSCs RTT model, we found that IL-6 is highly upregulated in RTT astrocytes, affecting neuronal homeostasis. We then hypothesize that IL-6 contributes to the early autistic phase of RTT. Thus, the main objective of this proposal is to better understand the role of IL-6 on the interplay between astrocytes and neurons in a human model. We will take advantage of a collection of RTT iPSC to generate different neural types to measure the impact of IL-6 in co-culture experiments. We will also work with brain organoids to test specific IL-6 blocking reagents in rescue experiments. If successful, our experiments will lead to a series of pre-clinical data in both mouse and human backgrounds that supports the use of IL-6 blockers in RTT clinical trials.