Unraveling the Role of Type I Interferons in Neurodevelopment: Insights from Human Brain Organoids

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Abstract:

Neurodevelopment is an intricate and extended process, beginning approximately two weeks after conception and persisting through to young adulthood in humans. While it is now evident that this process exhibits human specific features and is orchestrated by a combination of genetic and environmental influence, the precise underlying mechanisms remain to be elucidated.
Among these influences, the roles of immune signals are the most enigmatic. As a matter of fact, type I interferons (IFNs) are widely studied cytokines, initially recognized for their pivotal role in antiviral immune responses. Dysregulated type I IFNs have been suggested to contribute to neurodevelopmental defects, whether they are caused by in utero acquired infections or by genetic type I interferonopathies, mimicking those infections, such as Aicardi Goutières Syndrome (AGS) and Pseudo-TORCH syndromes. Yet, type I IFN treatments do not impair the growth of human brain organoids, in vitro models of human brain development, and provide neuroprotection against Zika and Herpes virus infections in these models. Furthermore, type I IFNs are now emerging as key regulators of brain homeostasis, since an interferon response is already observable in neural stem cells, where it controls stem cell homeostasis through regulation of mTORC1 activity and cell cycle. To delve into the molecular mechanisms underlying the functions of type I IFNs in normal development and disease conditions, we combine human stem cell-derived brain organoids, genetically engineered reporter systems of type I IFN signalling and CRISPR-Cas9 editing of IFN pathway components, to describe the differential regulation of IFN-α and β responses in human brain organoids. This approach allows us to gain valuable insights into the intricate interplay between the immune system and neurodevelopment, shedding light on potential therapeutic strategies for conditions marked by interferon dysregulation.