Biology Seminar

12:30 - 1:30 pm
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BGS 0153

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Humanized Models Of Microglial Development Shed Light On Viral Teratogenicity And Neurodegenerative Processes

The brain was once thought to be largely isolated from the immune system. This view is changing, as recent data suggest that peripheral and resident immune cells play complex roles in brain disorders. We devised human models of microglia-neuron interactions, and are using these models to understand how inflammatory triggers affect brain function. We worked to recreate microglial ontogeny in the dish, from human pluripotent stem cells, generating primitive macrophages resembling early microglia. Using novel tissue-engineering approaches including 3D co-cultures and cerebral organoids, we showed that their transcriptional profile and physiological behavior could approximate different stages of development, leading to their ability to dynamically survey the neuro-glial environment, and respond to injury or immune stimulation. Microglia are at the leading edge of our knowledge on the etiology of diseases such as Alzheimer's disease or Autism. Genes expressed uniquely in microglia have been identified by genome-wide association studies in those disorders, and functional impacts of allelic variations in those cells are largely unknown. Using the CRISPR toolkit, we can recreate such variants and interrogate our platforms to understand how these cells may participate in situations of inflammatory stress that precede, accompany, or terminate various degenerative disorders. As proof-of-principle, we have focused on the role of microglia in the early dissemination of the Zika virus to the fetal nervous system, and performed an unbiased CRISPR screen for host factors necessary for lethal infection of neural stem cells.