Epigenetic Changes Associated with Interferon γ Induced Transposable Element Expression in Microglia

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How Brain Immune Cells React to Ancient Viruses in Our DNA in Parkinson's Disease

With an aging population and a growing number of patients, the research on neurodegenerative diseases such as Parkinson's disease (PD) has become an important focus. PD causes progressive difficulties with movement and coordination that worsen over time. Further, PD is characterized by the loss of neurons and inflammation among other pathological processes. In recent years, the significant role of inflammation has become a focus, but many aspects still remain poorly understood. Microglia, as the resident immune cells of the brain, play a crucial role in inflammation in the brain. Emerging evidence suggests that an unexplored part of our deoxyribonucleic acid (DNA) plays an important role in many diseases as well as PD. Our DNA contains relics of ancient viral infections that infected our ancestors millions of years ago. Think of them as old 'computer files' that have been locked away and are normally harmless. These viral relics are kept switched off by a kind of molecular lock through specific molecules interacting with the DNA. These molecules, which control the lock, are grouped into activating and repressing types. This mechanism can be affected by different environmental factors, such as inflammation. If those viral relics are switched on in microglia, they may affect their behavior and disease progression. To study this mechanism, human microglia-like cells were used to model inflammation outside of the brain in a less complex environment. The microglia were exposed to an inflammatory signal found in the brains of PD patients and changes in activation of these viral relics in the DNA were mapped through different techniques. This showed that multiple of these viral relics were switched on directly or indirectly by neighboring 'files'. These findings provide new insights into inflammatory mechanisms in PD and may point towards future therapeutic targets.

Abstract

Introduction: Neuroinflammation is a key feature of neurodegenerative diseases, such as PD. Emerging evidence suggests that endogenous retroviruses (ERVs), epigenetically silenced relics of ancient viral infections, may become reactivated under inflammatory conditions and contribute to the inflammatory process and disease progression.

Background: Previous work from the Jakobsson group has shown a correlation between an interferon (IFN) response signature and ERV expression in microglia from PD post-mortem tissue. In vitro, IFN-γ stimulation has been shown to induce ERV activation in microglia. Understanding the pathways involved in this process, particularly the epigenetic mechanisms regulating ERV activation, may provide insights into potential therapeutic targets for PD.

Aim(s): The aim of this study was to describe ERV dysregulation in human induced pluripotent stem cell (hiPSC)-derived microglia under PD-associated inflammatory conditions, with a focus on the epigenetic changes at ERV loci induced by IFN stimulation.

Methods: A hiPSC-derived microglia model was used to model PD-associated inflammation using IFN-γ stimulation. The reproducibility and identity of this cell model were validated through flow cytometry, immunocytochemistry (ICC), reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) and bulk ribonucleic acid (RNA) sequencing. The inflammatory response and associated ERV dysregulation were studied using bulk RNA sequencing and epigenetic mapping through cleavage under targets and release using nuclease technique (CUT&RUN).

Results: A reproducible hiPSC-derived microglia model was successfully established across independent differentiation batches. IFN-γ stimulation induced a PD-associated inflammatory state with expected marker changes. Thirty significantly upregulated ERVs were identified, consistent with patterns previously observed *in vitro*. Locus-specific CUT&RUN analysis revealed changes in a permissive histone mark nearby ERV loci, suggesting upstream regulatory mechanisms either close at the ERV locus or in association with nearby genetic elements.

Conclusion: These findings describe mechanisms underlying the association between IFN signaling and ERV derepression in microglia, laying a foundation for understanding the epigenetic mechanisms linking neuroinflammation and ERV dysregulation in PD.

Keywords: Transposable elements, Neuroinflammation, Parkinson's disease, Microglia and Epigenetics