Publishable Summary

Infection by the human herpes simplex virus-1 (HSV-1) is among the most common childhood infections usually causing cold sores. Although HSV-1 usually results in mild disease, very rarely, infection can be life threatening. One such rare but serious complication is a brain infection known as encephalitis. Childhood herpes simplex encephalitis (HSE) is known to result from genetic deficiencies of a particular antiviral pathway (the TLR3-IFN pathway). Patients with these deficiencies are unable to produce protective factors (IFNs) following virus infection. However the known genetic deficiencies account for >10% of HSE cases in our study cohort. There are two main objectives to this proposal:

(i) To identify other gene(s) responsible for protection against HSV-1 infection in childhood HSE patients,
(ii) To explore anti-HSV1 immunity in the neuronal cells of HSE patients.

We have focused on studying one particular patient with HSE, P1, whose cells showed a TLR3 pathway defect. We have successfully identified a novel gene, using whole exome sequencing technology, previously not known to be involved in the HSE-causing TLR3 pathway. P1 is heterozygous for this missense mutation found in a gene involved in the endoplasmic pathway. The mutation is novel and predicted to have a deleterious impact on the protein. Initial studies knocking down the gene in control cells show impaired production of protective antiviral IFNs following stimulation of the TLR3 pathway. Confirmation and further characterization of the gene is ongoing.

There have been unexpected delays in the generation of neuronal cells, and we have shifted our focus to explore the role of another cell autonomous antiviral mechanism in HSV1 immunity: autophagy. Autophagy is involved in the recycling of damaged cellular components, and in elimination of unwanted viral infections. Recently, genes in the TLR3 pathway were also found to play a role in the autophagy pathway. However the role of autophagy has not been studied in HSE patients. We proposed that autophagy plays an important role in preventing brain damage caused by HSV1 infections. We have studied the process of autophagy following viral infection in these patients' skin cells to understand its role in disease. We plan to further study the role of this pathway in the patients' brain cells using a state-of-the-art method of culturing skin cells into brain cells to study patients' brain cells in a non-invasive manner.

The identification of genes and pathways involved in disease will improve our understanding of human herpes virus infections. Results from this study may lead to the development of new drug targets for HSV1. It may also lead to the development of therapies in the prevention of brain or nerve damage which remains a major cause of morbidity in HSV1 diseases. The results of the project are of high impact and have been the subject another grant proposal that I have been successfully awarded. This not only demonstrates the value of the work but has also enabled me to fully integrate into the Host institute as an independent researcher.