TISSUE DERIVED DENDRITIC CELLS AND THE IFN PATHWAY

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Type I and III IFNs are vital components of the hosts early innate immune response to viral infection. The release of IFNs primes the adaptive arm of the immune system and importantly helps to limit further viral replication by inducing the expression of interferon stimulated genes (ISGs) in neighbouring cells. However, in order to establish an initial infection HIV is able to manipulate the IFN pathway. Previous studies have shown that HIV inhibits IFN-β production in CD4+ T cells by degrading IRF3, the transcription factor that binds to the IFN-β promotor. Similarly, we have shown that monocyte derived dendritic cells (MDDCs) and macrophages do not produce IFN-β in response to HIV due to an inhibition of upstream TBK1 phosphorylation, resulting in a failure of IRF3 to translocate to the nucleus. This ability of HIV to inhibit IFN in dendritic cells may help the virus to establish a toehold infection in anogenital mucosa. All of the work to date has been done in blood derived model systems, however the main route of HIV infection is via mucosal tissue transmission. We therefore aim to extend our previous studies to examine the IFN response to HIV in tissue-derived DCs which are a major target after sexual transmission.

Langerhans Cells (LCs) are the main DCs present within the anogenital epidermis, however our laboratory has recently described a new subset of DCs found in healthy uninflamed epidermal tissue; CD11c+ epidermal DCs. These cells express higher levels of the HIV co-receptor CCR5 and are more permissive to infection compared to LCs. Using digital droplet PCR and flow cytometry we are currently investigating the ability of LCs and CD11c+ epidermal DCs to produce IFN-β upon HIV infection *ex vivo*. If, similar to MDDCs, these tissue-derived DCs fail to produce IFN-β in response to HIV, we furthermore aim to pinpoint the possible blockade in the IFN pathway, looking at phosphorylation of TBK1 and cellular localisation of IRF3.