

## **Polymorphisms in the IRF1 gene associated with reduced HIV susceptibility and their impact on plasma and cervical lavage cytokine/chemokine expression**

A. Sivo<sup>1</sup>, R.-C. Su<sup>1</sup>, J. Lajoie<sup>1</sup>, J. Kimani<sup>1,2</sup>, W. Jaoko<sup>2</sup>, K. Fowke<sup>1,2</sup>, F.A. Plummer<sup>1,3</sup>, T.B. Ball<sup>1,2,3</sup>

<sup>1</sup>University of Manitoba, Medical Microbiology, Winnipeg, Canada, <sup>2</sup>University of Nairobi, Medical Microbiology, Nairobi, Kenya, <sup>3</sup>National Microbiology Laboratories, Public Health Agency of Canada, Winnipeg, Canada

**Background:** Interferon Regulatory factor 1 (IRF1) is a transcriptional activator of interferon genes and interferon inducible genes and plays a crucial role in host antiviral immunity and HIV replication. Previous work has shown association of three polymorphisms in IRF1 with decreased acquisition of HIV-1 infection in a Kenyan female sex worker cohort. Peripheral blood mononuclear cells from individuals with protective IRF1 genotypes show reduced endogenous IRF1 expression and impaired transactivation of HIV-1 LTR when infected with a single-cycle HIV-1 VSV-G pseudovirus construct expressing a luciferase reporter gene insert, suggesting a limited ability to support HIV replication. This study will characterize the effect of the identified IRF1 polymorphisms on plasma and cervical lavage (CVL) cytokine/chemokine expression, focusing on IRF1's function in regulating the expression of host immunological genes and the impact this may have on susceptibility to HIV-1 infection.

**Methods:** We investigated the effect of IRF1 polymorphisms on the expression of 22 different cytokines/chemokines (IL1 $\beta$ , IL2, sIL2R $\alpha$ , IL6, IL8, IL10, IL12p70, IL15, IL17, sCD40L, Fractalkine, IFN $\gamma$ , IP10, MCP1, MCP3, MIP1 $\alpha$ , MIP1 $\beta$ , TNF $\alpha$ , ITAC, MIG, MIP3 $\alpha$  and MIP3 $\beta$ ) in plasma and CVL samples from female sex-worker cohort from Nairobi Kenya. Cytokine/chemokine levels were measured using Milliplex MAP multiplex kit (Human Cytokine/chemokine panel I and III from Millipore, Billerica, MA) and analyzed on the BioPlex-200 (Bio-Rad, Mississauga, ON, Canada).

**Results:** We observed significantly increased expression of IL15, IL17 and IFN $\gamma$ , and decreased expression of MIP1 $\alpha$  in the plasma samples of individuals with protective IRF1 genotypes. Additionally, we observed significantly higher expression of IL2, IL15 and IFN $\gamma$  in CVL samples from individuals with protective IRF1 genotypes, compared to the individuals without the protective IRF1 genotypes.

**Conclusion:** The observed increase in anti-viral cytokine expression in the plasma and CVL from the female sex workers with protective IRF1 genotypes could represent an important mechanism in preventing the establishment of HIV infection. It is important to fully characterize the effect of IRF1 polymorphisms as this will further the understanding of natural resistance to HIV infection and can contribute to the development of novel prophylactic or therapeutic modalities.