ImmunoTools *special* Award 2015

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Regulation of IFN-γ production in human tuberculosis. Searching for new biomarkers.

Tuberculosis remains a substantial global health problem. There were an estimated 8.6 million new TB cases in 2012 with 1.3 million TB deaths. Protective immunity requires the generation of T-helper 1 (Th1) cytokine responses and IFN-γ, which activates macrophages to inhibit mycobacterial growth. Persons with mutations linked to IFN-γ signalling have increased susceptibility to mycobacterial infection and disseminated infection after BCG vaccination *(Cunningham JA, Int J Tuberc Lung Dis 2000; 4:791; Newport MJ, N Engl J Med 1996; 335:1941)*. Regulation of the IFN-γ gene is complex, involving multiple transcription factors that bind to the proximal and distal promoter elements, including members of the cyclic adenosine monophosphate response element binding protein (CREB)/activating transcription factor family. It was previously demonstrated that CREB increased IFN-γ secretion to *M. tuberculosis* by binding to the IFN-γ proximal promoter *(Samten B, J Immunol 2002; 168:3520)*. We have previously shown that activation of signaling lymphocyte activation molecule (SLAM) in T cells from patients with tuberculosis increased CREB phosphorylation and IFN-γ production *(Pasquinelli V, J Immunol 2004; 172:1177; Pasquinelli V, J Infect Dis 2009; 199:661)*. In a recent work we found that activation of p38 and ERK MAPKs, in part through SLAM, mediates T-cell IFN-γ production in response to *M. tuberculosis*, a pathway that is defective in patients with tuberculosis *(Pasquinelli V, J Infect Dis. 2013; 207 (2):340)*.

The goal of our group of work is the elucidation of the mechanisms for reduced IFN-γ production in individuals who develop tuberculosis. We think that these findings will enhance our knowledge of disease pathogenesis, contributing to a better understanding of the immune response to this and others intracellular pathogens. Moreover since, DNA sequence variations [copy number variations, single nucleotide polymorphisms (SNPs) and microsatellite repeats] play an important role in susceptibility/resistance to tuberculosis and other infectious diseases like malaria and HIV we also studied the genetic variation in the host that could lead to reduced IFN-γ production. All the genetic studies are correlated with functional studies to evaluate

the impact of the SNP on the generation of a specific immune response against *M. tuberculosis*. Moreover, one of the goals of this line of work is found new genetic biomarkers of susceptibility or disease severity. Identification of genes that mediates susceptibility to tuberculosis is an important step in resolving the complex etiology of the disease.

Finally we have a new line of work in collaboration with Dr. Carolina Cristina to study the role of IFN-γ and IL-17 in the pathogenesis of prolactinomas. Since this project involves the use of a mouse model we also request some anti-mouse antibodies.

For our current work studying the immune response against *M. tuberculosis* we use recombinant cytokines as IFN-γ, IL-17, IL2, IL-10, TNF-α, among others. We also use blocking antibodies for this cytokines in order to regulate de cytokine microenvironment. We also perform ELISA and intracellular flow cytometry for surface markers and intracellular proteins. We use antibodies against CD4, CD3, markers for memory T cell population, transcription factors as T-bet, GATA-3, CREB. We are also working with macrophages to see the impact of some signalling pathways and costimulatory molecules (SLAM, PD-1, ICOS) on macrophage activation and microbicidal activity.

Get the ImmunoTools Award will be of great help for our research and will allow us to move forward with the project and continue growing in our new laboratory at the UNNOBA University.

ImmunoTools *special* AWARD for **Virginia Pasquinelli** includes 25 reagents

FITC - conjugated anti-human CD3, CD8, CD45RO, CD95, Control-IgG1, Annexin V,

PE - conjugated anti-human IFN-gamma, TNFa, Control-IgG1,

APC - conjugated anti-human CD4, CD14, Control-IgG1,

human TNFa ELISA-set for 96 wells (3 reagents),

recombinant human cytokines: rh IFNgamma, rh IL-1beta /IL-1F2, rh IL-4, rh IL-12, rh IL-17A, rh TNFα,

FITC - conjugated anti-mouse CD4,

PE - conjugated anti-mouse CD3e,

recombinant mouse cytokines: rm IFNgamma, rm IL-17A, rm TNFa, rm VEGF

DETAILS more AWARDS