ImmunoTools *special* Award 2015

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Evaluation the role of STAT3 on CD8 T cells during RSV infection

Respiratory Syncytial Virus (RSV) is ubiquitous in the environment and can cause severe infection in children and the elderly. Acute bronchiolitis caused by RSV is the most common disease in children in the first two years of life, with great impact on hospitalizations and high costs to the health system. Children with higher risk of severe disease are premature infants, newborns with bronchopulmonary dysplasia and infants with congenital heart disease. Some authors estimate that the mortality rate in premature infants hospitalized with RSV reaches 5%. An effective vaccine has not been developed. Currently, there are few available prophylactic treatments, such as the monoclonal antibody palivizumab, but at high cost. Thus, the development of new treatments and a RSV vaccine is essential.

Specific CD8 T cells are involved in RSV infection and improving the elimination of the virus. However, primary RSV infection does not confer a sustained and effective protective immune response and re-infection these viral strains are commonly reported. Respiratory syncytial virus has been shown to inhibit generation of memory CD8 T cells specific for a particular virus in the respiratory tract. The development of new vaccines and immunotherapies against RSV further depends on a better understanding of the molecular mechanisms involved in virulence factors responsible for pathogeneses of the virus and the consequent lack of protective $CD8^+$ T cell memory response.

Recently it has been shown that mutation in the protein STAT3 (signal transducer and activation of transcription 3) prevents the formation and function of CD8 memory T cells. The cytokine IL-21 is important for the development of memory CD8 T cells and performs this role by STAT3 activation. Structurally STAT3 protein has an amino terminal conserved region of the molecule responsible for tetramerization a DNA binding domain with a sequence-specific palindromic region

activated by IFNγ and SH2 region responsible for receptor recruitment. The STAT3 activation occurs through the phosphorylation of a tyrosine (Y705) or a serine (S727).

Our hypothesis is that RSV inhibits the activation of STAT3 and thus contributing to the absence of generation of specific CD8 T cells in the infection.

The aim of this project is to evaluate the role of STAT3 and IL-21 on CD8 T cells differentiation during RSV infection. The main questions we intent to answer are:

- Does RSV modulate STAT3 in human monocytes, CD8 T cells and human monocyte derived dendritic cells (mdDC)?
- Does IL-21 treatment increase STAT3 in human monocytes, CD8 T cells and mdDC and modulate the function of these cells during RSV infection?
- Does STAT3 inhibition with a specific inhibitor modulate murine CD8 T cells memory differentiation after co-culture with RSV infected bone marrow derived dendritic cells (BMDC)?

Selected reagents from ImmunoTools would be used for differentiation of dendritic cells from human monocytes or mice bone marrow, and for analyzes of CD8 T cells responses:

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includes 25 reagents

FITC - conjugated anti-human CD8, CD11b, CD86

PE - conjugated anti-human IFN-gamma, CD27

PerCP - conjugated anti-human CD3, HLA-DR, CD45RA

APC - conjugated anti-human CD44, CD11c

recombinant human cytokines: rh GM-CSF, rh IL-4, rh IL-21, rh TNFα

human ELISA-set for 96 wells, human TNF-a, human IL-12p40 total (detect IL-23 as well) (each 3 reagents)

FITC - conjugated anti-mouse CD3e

PE - conjugated anti-mouse CD8a

APC - conjugated anti-mouse CD44

recombinant mouse cytokines: rm IL-4, rm GM-CSF DETAILS more AWARDS