ImmunoTools *special* Award 2014

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The role of RNA editing in autoimmune diseases.

RNA editing is the co- or post-trascriptional modification of RNA which results in the insertion, deletion or substitution of nucleotides. The most important mechanism that leads to mRNA editing is the hydrolytic C-6 deamination of adenosine to yield inosine [1]. Inosines are subsequently recognized as guanosine by the translation machinery. This covalent modification of double-stranded RNA (dsRNA) is mediated by specific enzymes, such as ADAR1 and ADAR2. The human ADAR1 gene transcribes two main isoforms: a constitutively expressed truncated 110-kDa protein and an interferon-inducible 150-kDa protein. The ADAR2 gene transcribes constitutively expressed 80-kDa protein. RNA editing plays an important role in the regulation of gene expression; in fact it can correct, extend or diversify the information encoded within the corresponding genomic sequence, altering the function of different RNAs. The mRNA of the genes encoding mammalian glutamate receptors (gluR) [2], 5-hydroxytryptamine (5HT) serotonin receptors [3], ADAR2 are frequently subject to ADAR1- and ADAR2-mediated adenosine deamination. It is not well understood the effect of RNA editing in disease pathogenesis. However, in systemic lupus erythematosus (SLE), an autoimmune disorder, it was recently discovered mRNA transcript editing and up-regulation of the 150-kDa ADAR1 in T lymphocytes, induced by constitutive expression of interferons (IFN) [4]. Probably, this upregulation of ADAR1 contributes to the immunopathogenesis of SLE, because it leads to abnormal gene regulation. Moreover, altered expression of other RNA editing genes, such as ADAR2 and APOBEC3A, has been observed in T cells, peripheral blood mononuclear cells (PBMC) and natural killer (NK) cells of SLE patients [4,5]. Analyzing patients with Aicardi-Goutières syndrome, have been identified mutations in ADAR1 that cause this autoimmune disease [6].

The aim of my work is to analyze the expression of ADARs, in particular ADAR1, and to investigate an altered expression of ADARs in pathological conditions. To this regard, firstly I will isolate PBMC from blood samples of healthy individuals and patients with autoimmune diseases such as Multiple Sclerosis (MS), Ankylosing Spondylitis (AS) and Psoriasic Arthritis (PA), and I will stimulate them using interferon. After 24 hours, the PBMC will be harvested and stained with different cellular markers of T cells (α-CD3, α -CD4, α -CD8 and α -CD56) to characterize, by flow cytometry, the population involved in the modulation of ADARs expression. According to the population identified, I will activate PBMC with appropriate stimuli, depending on the type cells: I could use IFN-γ and IL-2 to stimulate T lymphocytes or IL-12 and IL-15 to stimulate NK cells. The activation of the cells will be monitored by

staining with α -CD25, α -CD69, α-HLA-ABC and α -HLA-DR. The altered expression of ADARs in patients, compared with controls, might affect the function of these enzymes, causing iper-editing or hypo-editing of specific transcripts involved in the modulation of T cell functions. Therefore, the RNA editing could be a new candidate epigenetic mechanism implicated in the gene regulation and immune response in autoimmunity.

References

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