ImmunoTools *special* Award 2014

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The adrenomedullin system in human thymus: a new pharmacological target in autoimmunity mechanisms.

Adrenomedullin (ADM) is a multifunctional peptide which exerts, through an autocrine/paracrine mode of action, multiple biological effects [1], including the regulation of blood pressure, cell growth and differentiation, modulation of hormone secretion, central nervous system functions and the potentiation of host defences against microbes [2,3]. ADM exerts its biological effects by interacting with a functional receptor formed by the combination of the calcitonin receptor-like receptor (CRLR), a 7-transmembrane G protein-coupled receptor (GPCR), with Receptor Activity-Modifying Protein 2 (RAMP2), which dictates its ligand binding specificity.

The thymus provides a variety of specialized microenvironments that support the production of self-tolerant T cells starting from immature precursors [4]. Each maturation event of T cells takes place in a discrete region of the thymus and relies on the interaction of thymocytes with specialized thymic epithelial cells (TECs). Developing thymocytes and TECs establish a mutual “cross talk”, governed by several cytokines and other factors, that is necessary for the functional maturation of both types of cells [5].

There is a growing appreciation of the importance of ADM in the immune system function. In particular, a protective role of adrenomedullin has been demonstrated in several autoimmune diseases, e.g. multiple sclerosis [6] and rheumatoid arthritis [7], but the thymic events involved in this effect have not yet been investigated.

In our laboratory we have for the first time demonstrated that both ADM and its receptor proteins CRLR and RAMP2 are expressed in human thymus [8], mostly in TECs. Our hypothesis is that ADM exerts its protective role in autoimmune diseases by controlling the

release of cytokines in the thymic microenviroment. We are mainly interested in the differentiation of Th17, T cells which, by producing IL-17, contribute to inflammation and autoimmunity. The inhibition of Th17 differentiation can lead to an increase in phenotypically mature and functionally stable regulatory T cells (Tregs), which are involved in protection against autoimmunity.

Therefore, the aim of this project is to investigate whether the ADM system in thymus is involved in the generation of immunological tolerance, which may open new avenues to the management of autoimmune diseases.

These experiments will be conducted on cells from both patients undergoing thymectomy and animal models of autoimmune diseases.

Therefore, the ImmunoTools selected products would be of great benefit to this project as they would be used to: 1) sorting thymocytes into subclasses, which are defined by the expression of CD3, CD4 and CD8; 2) verifying the effect of ADM on cytokine release from thymic cells by means of ELISA tests; 3) analyzing the Th17/Treg balance by measuring the cytokines released by these cells; 4) measuring the vitality and apoptosis of thymic cells after their stimulation with pro-inflammatory cytokines.

References

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4) Anderson G, et al. (2006) Immunol Rev 209: 10-27.
5) Anderson G and Takahama Y. (2012) Trends Immunol 33: 256-263
6) Pedreno M, et al. (2014) Brain Behav Immun 37: 152-63
7) Gonzaley-Rey E, et al. (2007) Am J Pathol. (1): 263-71
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ImmunoTools *special* AWARD for **Giovanna Paliuri** includes 20 reagents

human IL6 ELISA, human IL10 ELISA, human TNFalpha ELISA-set for 96 wells, (each 3 reagents),

recombinant human cytokines: rh TNFalpha, rh IFNgamma, rh IL17A, rh IL17F, rh IL6, rh EGF, rh TGF-beta3,

CD4 FITC / CD3 PE / CD8 PerCP

recombinant mouse cytokines: rm IFN gamma, rm IL6, rm TNFalpha

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