ImmunoTools *special* Award 2014

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Analysis of B lymphocytes subsets in CVI and autoimmune disease.

Novel developments in gene discovery and increased knowledge in the mechanisms that govern immune functions have resulted in the identification of several novel primary immunodeficiency (PID) syndromes.

Many of such PIDs revealed unexpected features of autoimmune diseases, and we have observed this in a proportion (10-20%) of our cases, represented by Common variable immunodeficiency (CVID), the most clinically important PID in adults. Although therapy with intravenous or subcutaneous immunoglobulins reduces the incidence of acute infections, replacement therapy does not allow the management of a series of respiratory complications whose importance is emerging for prognosis and quality of life, including asthma, COPD, interstitial lung diseases and lung granulomatosis. CVID patients with granulomatous disorders have B lymphopenia with distinctive absence of memory B cells, $CD21^{-low}$ and clinical features of splenomegaly and autoimmunity.

The recent discovery of a B regulatory subset of lymphocytes, with the characteristics of transitional (T2) cells (identified by $CD38^{++}$ $CD24^{pos}$), able to produce modulatory cytokines (mainly IL-10) and the publication of their dysfunction in some systemic autoimmune diseases (e.g. SLE), caught our attention for the possible role of the presence or activity of such B cells in a subset of CVID as well as in other autoimmune diseases. We have preliminary data on these cells in Rheumatoid arthritis patients and our goal would be to extend the study of this rare but essential subset in other connective tissue diseases such as Systemic sclerosis and Sjogren's syndrome, as well as in all PID cases, mostly adult onset CVID. Systemic sclerosis is a devastating fibrosing disease affecting not only the skin but also visceral organs, including lung and intestine, with a poor prognosis and scarce response

to existing therapy. Sjogren's syndrome is an exocrine gland targeted autoimmune disease which carries risk of B cell lymphoma originating in salivary glands. In both diseases B lymphocytes are suspected to be at the forefront of the immune disorder, but their role is still largely not clear. Anti-CD20 therapy has been attempted with mixed results.

The phenotype of B and T cells from peripheral blood will be analysed using 4-color flow cytometry and cytokine production assessed by intracellular staining and confirmed by multiplex ELISAs.

The award we are seeking would give us freedon to analyse more patients than we are ready to study now with present grants. A total of 60 cases are expected to be studied in 1 year, and compared with at least 15 healthy controls. Data obtained, both percentages and absolute numbers/cu.mm using a dual platform method, will be statistically treated for all immune parameters and clinical variables, including disease, duration, use of drugs acting on immune system, age and sex. We expect to find some similarities for ratio of Breg to B cells, correlations between Bregs and Tregs, memory to naïve ratio in B and T subpopulations, with differences among diseases and with the control group. The results may give new insights in the pathogenetic role of B lymphocytes subsets both in CVID and in some systemic autoimmune diseases.