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Website: http://www.hsr.it/ricerca/divisioni-centri-istituti-e-programmi-di-ricerca/istituto-di-ricerca-sul-diabete-hsr-dri/regolazione-dell-immunita-adattiva/

Project description

Intended for the Basic and Applied Immunology and Oncology Curriculum

Title: **Role of follicular helper and follicular regulatory T cells in common variable immunodeficiency and autoimmunity**

Summary of Proposed Project. Common variable immunodeficiency (CVID) is the most common primary antibody deficiency (PAD), a serious clinical condition that if untreated leads to persistent and recurrent infections and increased risk of death. The only current therapy for patients with CVID is immunoglobulin (Ig) replacement which, however, treats the symptoms but not the real cause of the disease. Among the clinical features of CVID, autoimmune and inflammatory manifestations are the most difficult to treat because of insufficient knowledge regarding their cause and the response of patients to therapy. CVID can result from defects in B cells or it can be T-cell mediated. In the latter case, follicular helper T (TFH) cells, that drive T cell-dependent humoral immunity in germinal centres (GCs), were shown to underpin CVID development. Aberrant TFH cellularity or function may also result in autoimmunity (AI), suggesting it could account for the autoimmune manifestations also in patients with CVID. Follicular regulatory T cells (TFR) are a recently characterized subset of lymphocytes that safeguard the function of TFH cells limiting AI and excessive GC reactions. The impact of TFR cells in CVID is completely unknown. It is possible that they are dysfunctional and promote AI or hyperactive over-inhibiting TFH cells and causing CVID progression. Thus, defects in TFH and/or TFR cells could be responsible for the development of CVID and could account for the autoimmune manifestations. In our clinic we have identified seven familial cases of CVID+AI with the aim to understand the role of TFH and TFR cells and the genetic underpinnings that drive the development of this complex disease. Hopefully this study will discover new genes that control the number and function of TFH and TFR cells, will generate new hypothesis on the natural history of CVID and AI and, most importantly, identify new therapeutic targets. With this proposal we aim to:

Specific aim-1: Characterize the quantity and quality of TFH and TFR cells in the peripheral blood and organs of patients with CVID+AI.
Specific aim-2: Determine the genetic mutation(s) and polymorphisms that affect TFH and TFR cell number and function driving CVID development and increasing susceptibility to AI.

Literature

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