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'Honeymoon' biomarkers in type 1 diabetes

Type 1 diabetes (T1D) is a metabolic disease that results from the autoimmune attack against insulin-producing β-cells in the pancreatic islets of Langerhans. The incidence of T1D among children is increasing in developing countries, particularly in children under the age of 15 years, with an overall annual increase estimated to be around 3-5% per year. The prevalence of this disease, its complications and the lack of effective curative and preventive strategies require the development of new therapies capable of induce long-term tolerance. An ideal immunotherapy should inhibit the autoimmune attack, avoiding systemic side effects and allowing islet regeneration to improve β-cell function. An important issue would be the stage of the administration of the therapy.

An interesting stage of the disease from an immunological and metabolic point of view is the 'honeymoon' phase. The 'honeymoon' refers to the period of time shortly following diabetes diagnosis, when insulin needs account for about 50% of the initial insulin requirement, achieving temporary insulin-independence in some cases. This period, usually lasting 7 months, is also called partial remission and suggests a 'rest' of β cells after the insulin treatment, and probably an attempt to restore immunological tolerance, to arrest the autoimmune reaction and an attempt of β cell mass regeneration. Nowadays, there are few studies about the immunological and metabolic phenomena occurring after insulinization during the 'honeymoon', but there is a clear consensus about the relevance of this period. Our group performed the first transcriptome study from pancreas and islets from diabetic patients [*Planas R, 2010*]. Significantly, one patient in 'honeymoon' period showed evident signs of immunoregulation and regeneration, as well as, an overexpression of innate immunity and inflammation genes that could establish a balanced and persisting autoimmune response. This profile fits well within the hypothesis of T1D as a

relapsing-remitting disease [*von Herrath M, 2007*] and offers a list of possible new biomarkers.

The hypothesis of this project is that the autoimmune process associated to T1D in the 'honeymoon' period is reflected in periphery through unknown biomarkers. Because of the complexity of the study of this disease, both for the asymptomatic period and for the difficulty in accessing the target organ, the finding of differential parameters of the 'honeymoon' period would be crucial to determine biomarkers of the disease progression and secondary complications, or even for therapeutic targets.

The main goal of this study is to perform a transversal and longitudinal study from now onset T1D patients to detect alterations in lymphocyte subsets molecular biomarkers (metabolic, inflammatory, or autoimmune) in the 'honeymoon' period. Blood samples will be obtained from T1D patients at disease onset, and 3, 6 and 12 months after. Lymphocyte subpopulations (naïve, memory, effector or regulatory T cells and naïve, transitional or memory B cells) will be characterized by flow cytometry. Inflammatory and immunoregulatory cytokines will be quantified by ELISA, as well as other molecules involved in the tolerance restablishment.

The clinical relevance of the identification of new biomarkers of 'honeymoon' in T1D and its correlation to other metabolic parameters resides in its translational potential to identify subjects at risk for secondary complications and to predict honeymoon length for the administration of immunotherapies.