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Fibroblast-Like Limbal Stem Cells (F-Lscs) as a Potential Tool to Promote Tolerance Induction in Autoimmunity Diseases

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Short Communication

Despite the countless and intensive research efforts, there is an increasing need to reverse the immunological dysfunctions on which any autoimmune disease is based. Recent evidences has shown in mesenchymal stem cells (MSCs) pleiotropic immune regulatory activities both *in vitro* and *in vivo* [1]. In particular MSCs seem to be receptive to inflammatory signals and able to mount peculiar tolerogenic immune responses, restoring the immune homeostasis. Unfortunately the immunosuppressive mechanisms mediated by MSCs are only partially understood with sometimes contradictory data available. Several *in vitro* data have demonstrated that the proliferation of T cells stimulated with either polyclonal mitogens, allogeneic cells or specific antigens is inhibited by MSCs through the arrest of lymphocytes in the G0/G1 phase of the cell cycle [2-4]. This non-classical form of anergy has been indicated as "tolerance arrest" of T cells [5]. In addition, MSCs have also been reported to influence the cytokine secretion profile of different T-cell subsets, causing decreased production of pro-inflammatory cytokines like interferon (IFN)-γ, tumor necrosis factor (TNF)-α and interleukin (IL)-6, IL-17, and increased levels of anti-inflammatory cytokines such as IL-4 and IL-10 [6-8]. Taken together, these results could indicate a possible MSC-mediated restoration of Th1/Th2/Th3 unbalance in all those pathologies that require the expansion of $Foxp3^+$ regulatory T cells, polarization of macrophages and T helper subsets and inhibition of antigen-presenting cells.

Recently, we isolated from the human eye a stromal fibroblast-like limbal stem cell (f-LSC) population characterized by the expression of several pluripotent stem cell markers, self-renewal ability and long-term maintenance of stem properties independently of donor age [9,10]. In addition, we found their natural immuno-privileged status to depend on both cell contact and soluble factors produced, as well as undetectable expression of the complete pattern of molecules required to fully activate T-lymphocytes (HLA-DR, CD80, CD86). We found numerous biologically active factors to be secreted from f-LSCs: growth factors, cytokines, chemokines and hormones. In particular, the most relevant immunosuppressive molecules expressed by f-LSCs included the IL-10, the transforming growth factor (TGF-β), prostaglandin E2 (PGE-2), soluble HLA-G (sHLA-G), the hepatocyte growth factor (HGF), Indoleamine-pyrrole 2,3-dioxygenase (IDO), nitric oxide (NO) and the Autoimmune Regulator (AIRE). These factors are all able synergically to orchestrate an immunosuppressive response even if an inflammatory environment is present.

This kind of background is typically described in autoimmune thyroid diseases (AITD), which comprise Hashimoto's thyroiditis (HT) and Graves' disease (GD). They are both characterized by reactivity to autoantigens causing, respectively, inflammatory destruction and autoimmune stimulation of the thyroid-stimulating hormone receptor.

In a recent application patent we reported the possibility of preventing inappropriate activation of autoreactive T lymphocytes collected from patients with Hashimoto's Thyroiditis (HT) through an *in vitro* coculture protocol (Patent Application #1020160000130565 filed on 12.23.16). During co-culture of peripheral blood mononuclear cells (PBMCs) with f-LSCs, T-lymphocyte reeducation occurred in a 4-hour time range. Notably, the hypo-immunogenicity of f-LSCs can revoke the need for human leukocyte antigen (HLA) matching in case of re-infusion of educated lympho-monocytes in HT patients. Therefore, this system optimizes the safety of the potential treatment of HT disease with autologous *in vitro* immune-modulated lymphocytes compared to the conventional immunosuppressive therapies and eliminates the ethical concerns associated with

other stem cell-based approaches. The same protocol could be tested in other autoimmune endocrine organ-specific diseases, such as Addison's syndrome, hypoparathyroidism, hypophysitis, Graves' disease, celiac disease, Type 1 diabetes and Autoimmune Poliendocrine diseases (SPA) where the single disorders combine with each other. Some attempts at Stem Cell Educator Therapy induced by umbilical umbilical cord blood-MSCs have already been described in Type 1/2 Diabetes and Alopecia Areata [11-13]. Unfortunately, numerous limitations in the use and collection of CB-MSCs make them an unsuitable source of stem cells for their use on a massive scale. Our approach could definitely provide a tool for lasting reversal of autoimmunity in patients with HT or other immunological disorders, pulling down the annual public costs due to their permanent therapeutic monitoring and medical care. Furthermore, as an easily accessible source of autologous stem cells with a minimal and well-established surgical procedure, f-LSCs represent an excellent chance for use in clinical applications.

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