PROJECT

Supervisor:	Silvia Gregori
Title:	Exploiting DC-10 activity to modulate immune response
Curriculum:	Basic and Applied Immunology and Oncology

Link to the personal page of the University or relevant hospital site website: ----------

https://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy/mechanisms-of-peripheral-tolerance/silvia-gregori.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Immune tolerance is the physiological mechanism that prevents an immune response to self and non-dangerous antigens. Its disruption can lead to autoimmune diseases, whereas excessive activation of tolerogenic mechanisms may allow malignant cells to evade immune surveillance. In both contexts, the key pathogenic cellular mechanisms remain poorly defined. IL-10-producing tolerogenic dendritic cells (DC-10) are naturally occurring tolerogenic myeloid cells with a unique capacity to induce Type 1 regulatory T (Tr1) cells [1, 2]. Notably, in vivo, DC-10 levels correlate positively with states of enhanced immune tolerance and negatively with conditions characterized by impaired tolerance and cancer progression [3-5].

Rationale and hypothesis

Cell therapy has been extensively investigated for tolerance induction, but safety concerns, high costs, and inconsistent efficacy have prompted a shift toward in vivo strategies that promote regulatory cell differentiation and function within their natural microenvironment [6, 7]. We have previously defined the molecular and metabolic circuits that control the induction and suppressive activity of DC-10 [8], thereby establishing the mechanistic basis for targeted immunomodulation. Building on these insights, we will develop tools to target in vivo myeloid cells and enhance their tolerogenic functions in the context of autoimmunity or blunt their immunomodulatory activity in the context of solid tumors.

Objectives and specific aims

This project aims to elucidate and therapeutically exploit the mechanisms governing the induction of DC-10 and related regulatory pathways *in vivo*. We identified the following Specific Aims:

Aim 1. To develop engineered nanoparticles capable of targeting DC-10 *in vivo*.

We will exploit DC-10-derived extracellular vesicles characterization to develop engineered nanoparticles capable of targeting myeloid cells *in vivo* and inhibiting their protolerogenic differentiation and/or function. Specifically, we will generate engineered extracellular vesicles and/or hybrid lipid nanoparticles (LNPs) loaded with molecular cargoes inhibiting tolerogenic functions, tailored for selective targeting of monocytes. Their ability to drive monocyte differentiation toward a proinflammatory phenotype will be evaluated *in vivo*.

Aim 2. To define the immunosuppressive role of DC-10 in Hepatocellular carcinoma and target it to inhibit tumor growth.

We will define the frequency/phenotype of DC-10 in peripheral blood, as well as the frequency/phenotype, and functions of tumor-infiltrating DC-10 in Hepatocellular carcinoma (HCC) patients. In parallel, we will define the role of DC-10 in tumor progression in preclinical HCC models and determine whether targeting myeloid cells/DC-10 with engineered particles generated in aim 1 enhances anti-tumor immunity and tumor clearance in preclinical models.

Expected outcomes

We will develop innovative strategies to precisely inhibit DC-10 function *in vivo*. These strategies may provide new tools for effective myeloid targeting *in vivo* immunomodulation and pave the way for the development of novel Immunotherapeutics for cancer.

Skills that the student should acquire (max. 600 characters including spaces):

The student will learn how to design experiments, critically analyze and interpret data, formulate scientific hypotheses, and create new experiments to test those hypotheses. She/He will also receive training to develop communication skills, including presenting and discussing data during lab meetings and public presentations of their projects. Additionally, the student will gain technical skills in cellular and molecular biology, such as culturing primary cells, conducting immunological assays, designing and producing lentiviral vectors, and using in vivo preclinical models.

References (max. 15)

1. Gregori S, Tomasoni D, Pacciani V, Scirpoli M, Battaglia M, Magnani CF, et al. Differentiation of type 1 T regulatory cells (Tr1) by tolerogenic DC-10 requires the IL-10-dependent ILT4/HLA-G pathway. Blood 2010; 116:935-44.

2. Amodio G, Comi M, Tomasoni D, Gianolini ME, Rizzo R, Lemaoult J, et al. Hla-g expression levels influence the tolerogenic activity of human DC-10. Haematologica 2015; 100:548-57.
3. Amodio G, Mandelli A, Curto R, Rancoita PMV, Stabilini A, Bonfanti R, et al. Altered Frequency and Phenotype of HLA-G-Expressing DC-10 in Type 1 Diabetes Patients at Onset and in Subjects at Risk to Develop the Disease. Front Immunol 2021; 12:750162.
4. Xu DP, Shi WW, Zhang TT, Lv HY, Li JB, Lin A, et al. Elevation of HLA-G-expressing DC-10 cells in patients with gastric cancer. Hum Immunol 2016; 77:800-4.
5. Passerini L, Amodio G, Bassi V, Vitale S, Mottola I, Di Stefano M, et al. IL-10-producing regulatory cells impact on celiac disease evolution. Clin Immunol 2024; 260:109923.
6. Morali K, Giacomello G, Vuono M, Gregori S. Leveraging current insights on IL-10-producing dendritic cells for developing effective immunotherapeutic approaches. FEBS Lett 2024.
7. Passeri L, Marta F, Bassi V, Gregori S. Tolerogenic Dendritic Cell-Based Approaches in Autoimmunity. Int J Mol Sci 2021; 22.
8. Avancini D, Testori A, Fresolone L, Andolfi G, Vuono M, Martinelli V, et al. Aryl hydrocarbon receptor activity downstream of IL-10 signaling is required to promote regulatory functions in human dendritic cells. Cell Rep 2023; 42:112193.