Ds are innate immune cells that play a central role in linking innate and adaptive immunity, as they are potent, professional APCs with the unique ability to prime naive T cells in vivo. On the other hand, DCs are also critical in the maintenance of immune tolerance against self-antigens to prevent the development of autoimmunity [1]. Indeed, tolerogenic DCs endowed with immunoregulatory functions are important for limiting immune responses against commensal pathogens and for silencing fetal alloantigens encoded by paternal genes during pregnancy to allow survival and growth of fetus [2].

Besides the favorable effects of tolerogenic DCs in these physiological conditions, immunoregulatory DCs can also give rise to deleterious and adverse reactions during the course of chronic viral infections and tumors, where the presence of these cells may hamper the development of optimal and antigen-specific adaptive immune responses [3, 4]. Low costimulatory potential, high expression of inhibitory molecules, and a preferential cellular polarization toward the production of anti-inflammatory cytokines are among the factors contributing to the establishment of the regulatory functions of tolerogenic DCs [1].

The lack of DC activation with retention of an immature phenotype characterized by low levels of costimulatory molecules is the typical strategy undertaken by DCs to maintain tolerance upon exposure to self-antigens in physiological conditions. The accumulation of immature DCs or partially mDCs has been reported to enrich the microenvironment of many types of cancer, thus suggesting that preventing a full maturation of DCs could be an escape mechanism exploited by tumor cells to evade immune surveillance [5].

On the contrary, tolerogenic mDCs express adequate levels of costimulatory molecules, although they fail to activate T cells, as these regulatory DCs express inhibitory molecules and preferentially produce anti-inflammatory cytokines. The best-characterized inhibitory receptors expressed on tolerogenic DCs are ILT-2, ILT-3, and ILT-4, which are considered key regulators of DC functions. ILT molecules display a long cytoplasmic tail containing ITIMs that mediates endogenous-negative signaling through inhibition of NF-κB activation. By interacting with yet-unknown exogenous ligands present on activated T cells, ILT molecules can also suppress T cell proliferation in response to cognate antigen and promote the conversion of activated T cells into Tregs [5]. Other inhibitory molecules expressed on tolerogenic DCs include IDO and nonclassical HLA-G. IDO is an immunoregulatory enzyme that promotes immune tolerance in many physiological and pathological conditions, mainly through the induced expansion of Treg. HLA-G belongs to class I molecules of the MHC-I and binds the inhibitory receptors ILT-2, ILT-4, and killer Ig-like receptor 2DL4 (KIR2DL4), whose functions are oriented exclusively toward the inhibition of several immune cell effector functions (such as cytotoxicity and cytokine production) and the establishment of immunological tolerance. Regarding DC functional properties, HLA-G has been shown to modulate antigen uptake and presentation, migratory capacity, expression of costimulatory molecules, and cytokine production. First described to be a key player in promoting maternal-fetal tolerance, the surface expression of HLA-G has been reported to be beneficial also in the context of transplantation, as it protects transplanted organs from immune destruction. In contrast, HLA-G may play a detrimental role during the course of infections and cancer, where it can promote tolerance to virus-infected or tumor cells [6].

Several pharmacological and biological agents have been shown to promote the development of tolerogenic DCs. In vivo, immunoregulatory DCs can arise from DCs resident in a microenvironment characterized by a tolerizing milieu, such as mucosal or immune-privileged tissue sites. In vitro, several compounds have been used successfully to generate tolerogenic DCs from hematopoietic precursors. Indeed, IL-10, TGF-β, PGE2, histamine, and its precursors, thrombo- poietin, vitamin D3, and a large number of different cytokines, have been demonstrated to modulate DC maturation and favor their differentiation into tolerogenic DCs [7, 8].

In this issue of JLB, Švaiger and colleagues [9] add IFN-γ the list of cytokines able to induce the generation of immune-regulatory DCs. In particular, this study demonstrates that high doses of this proinflammatory cytokine can promote the maturation of DCs endowed with regulatory functions. IFN-γ is a prototype of the Th1-type cytokine, produced mainly by NK and T cells, with a crucial role in modulating innate and adaptive immune responses against

**Editorial: IFN-γ: a Janus-faced cytokine in dendritic cell programming**

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Abbreviations: ILT=Ig-like transcript, mDC=mature DC, Treg=regulatory T cell
In their manuscript, Švajger et al. [9] demonstrate that treatment of DCs with high doses of IFN-γ, similar to the ones produced by activated Th1 cells in an inflammatory microenvironment, induces the acquisition of regulatory features by DCs. The mechanisms characterizing the generation of such immunoregulatory DCs are the up-regulation of ILT-4 and HLA-G inhibitory molecules on the cell surface, the switch of cytokine production toward an increase of the IL-10/IL-12p70 ratio, impaired allostimulatory activity and a reduced ability to activate CTLs.

The disclosure of this novel mechanism in the context of a Th1-like environment contributes to explain how the functional status of DCs can control and limit cytotoxic responses, thus preventing undesired tissue destruction and aberrant inflammatory reactions.

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