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PLATELETS & THROMBOPOIESIS

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Platelet antigen-induced regulation in ITP

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Tregs maintain self-tolerance and, although they are significantly deficient in patients with ITP,[1-6] it now seems that their antigen-specific counterparts can be generated de novo from the patient's other nonregulatory T cells. This may set the future stage for platelet-induced cellular therapy as a treatment for ITP.

The immune system has evolved several interactive peripheral regulatory mechanisms to protect against autoimmunity, and it has become increasingly clear that $CD4^+CD25^+FoxP3^+$ T regulatory cells (Tregs) are an important component of this control.[7,8] Their importance in maintaining peripheral tolerance is exemplified by the observations, for example, that mutation of FoxP3 leads to widespread autoimmunity in the scurfy mouse and immune dysregulation, culminating in the X-linked syndrome (IPEX) in humans.[7,8] Treg deficiencies have been found in several autoimmune diseases including the autoimmune bleeding disorder, idiopathic thrombocytopenic purpura (ITP). It is currently thought that this deficiency is at the center of immune dysregulation and stimulation of autoimmune attack.[1-6]

Tregs can be generally divided into 2 flavors depending on their ontogeny and mode of action. For example, natural (n) Tregs are generated in the thymus and are generally anergic to antigenic stimulation but can effectively inhibit proliferation of $CD4^+$ T helper cells via direct cell contact.[7] Thus, the ability to isolate these nTregs holds the promise of immunosuppressive therapy, however, since they constitute only 3% of circulating $CD4^+$ T cells, their numbers are far too small to be clinically effective. On the other hand, inducible (i) Tregs can be generated in the periphery from nonregulatory $CD4^+CD25^-$ T cells and, although they share the phenotype and in vitro suppressive activities of nTreg, they are activated in an antigen-specific fashion. Nonetheless, although iTregs can be induced from $CD4^+$ T cells, less is known about whether these cells function in healthy subjects or more importantly, whether they could be expanded from the peripheral blood of patients with autoimmune diseases known to be associated with deficiencies in Tregs.[1-7] In this issue, Zhang and colleagues address the latter possibility by studying whether iTregs could be stimulated in vitro from the peripheral blood of patients with ITP and whether the in vitro expanded cells were functional.[9] What they found is fuel for the notion that ITP is not only a complex immunoregulatory disorder involving several cellular and soluble elements, but that perhaps an effective autologous cellular therapy for ITP could be developed.

The authors studied 41 newly diagnosed patients with chronic ITP. They found that platelet glycoprotein (GP)–specific induced iTregs could be generated de novo from nonregulatory $CD4^+CD25^-CD45RA^+$ cells and could mediate both antigen-specific and linked suppression of proliferating anti-platelet $CD4^+$ T helper cells in vitro. Using a series of culturing techniques, they more importantly demonstrated that the expanded iTregs mediated their suppressive effects on T cells by actually modulating the T-cell stimulatory capacity of dendritic cells (DCs). This modulating effect was dependent on the presence of TGF-β, a potent immunosuppressive and tolerance-inducing cytokine. In an attempt to determine how the iTregs modulated DCs, they performed a genome-wide assessment of the DCs using microarrays and found that Toll-like receptor, Notch, and TGF-beta signaling pathways were related to the DC's ability to invoke suppression. How these particular signaling pathways within the iTreg-modified DCs affect the changes in their T-cell stimulatory capacity is still not known but these pathways are known to be intimately associated with both pro- and anti-inflammatory responses. It may be that the balance between these intracellular DC pathways ultimately controls the development of platelet autoimmunity. These findings not only increase our knowledge of how platelet-specific T-cell responses are regulated in patients with ITP but they shed light on the potential of producing antigen-specific iTregs from the patients in vitro for the purpose of antigen-targeted cellular immunotherapy.

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