CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Repressing Immunity in Autoimmune Disease

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Central tolerance is a process mediated in the thymus and bone marrow, in which autoreactive, potentially pathogenic T cells and B cells, respectively, are eliminated during ontogeny. However, this process is not foolproof; some autoreactive cells escape it. Additional regulatory mechanisms and agents can keep such cells in check. Among these agents are regulatory T cells, which are therefore promising targets for treating autoimmune and inflammatory diseases.

Among subsets of regulatory T cells, those coexpressing the markers CD4, CD25, and FOXP3 have been well studied. These FOXP3-positive regulatory T cells are selected on the basis of self-reactivity in the thymus or induced in the peripheral tissues under the influence of antigen-presenting cells and cytokines. Another type of regulatory T cell, the type 1 regulatory T (Tr1) cell, is also found in the periphery. Tr1 cells express CD49b and LAG3, do not express FOXP3, and secrete the antiinflammatory cytokines interleukin-10, interleukin-21, and transforming growth factor (TGF) β.

The Tr1 cell has been tested as a therapeutic substrate in the clinic[1] but, like its FOXP3+ counterpart, the therapeutic preparation contained regulatory T cells specific for multiple antigens. A method to expand single antigen–specific regulatory T cells in vivo is currently lacking. Santamaria and colleagues[2] recently investigated such a method for the Tr1 cell, using nanoparticles coated with autoimmune disease–relevant peptides bound to major histocompatibility complex (MHC) class II molecules (pMHCII-NPs).

It is known that antigen presentation by antigen-presenting cells in the absence of costimulation by B7-1 and B7-2 molecules leads to T-cell anergy in the periphery. However, Santamaria and colleagues found that systemic injection of pMHCII-NPs both restored normoglycemia in a mouse model of autoimmune (type 1) diabetes and induced the expansion of antigen-specific Tr1-like memory T cells. They observed ameliorative effects on disease-related pathologic processes in other mouse models of autoimmune disease (experimental autoimmune encephalomyelitis and a mouse model of arthritis) when they used other pMHCII-NPs expressing autoimmune disease-relevant peptides. In experimental autoimmune encephalomyelitis, they found that systemic expansion of cognate Tr1 cells was associated with the restoration of motor function, reduced activation of microglia and macrophages in the cerebellum, and reduced demyelination of the spinal cord; in the mouse model of arthritis, they observed resolution of joint inflammation and destruction (Fig. 1). The effect was preserved regardless of the dominance of any one particular autoantigen and regardless of whether the antigen had been implicated in disease initiation or as a downstream target. The therapeutic benefits of nanoparticles coated with the autoantigens, represented by peptides on the pMHCII-NPs, were disease-specific and affected disease-relevant organs.

By what means do pMHCII-NPs expand Tr1 cells, and how do these Tr1 cells affect regulatory networks? The authors showed that the relevant Tr1 cells arise from antigen-experienced memory T helper type 1 cells, and their generation and proliferation depend on the presence of interferon-γ and interleukin-10 (Fig. 1). The presence of interleukin-10, TGF-β, and interleukin-21 but not interferon-γ was required for Tr1 cells to suppress disease. In addition, Tr1 cells enhanced interleukin-10–producing regulatory B cells in an interleukin-21–dependent manner; the therapeutic effect of these regulatory B cells syner-

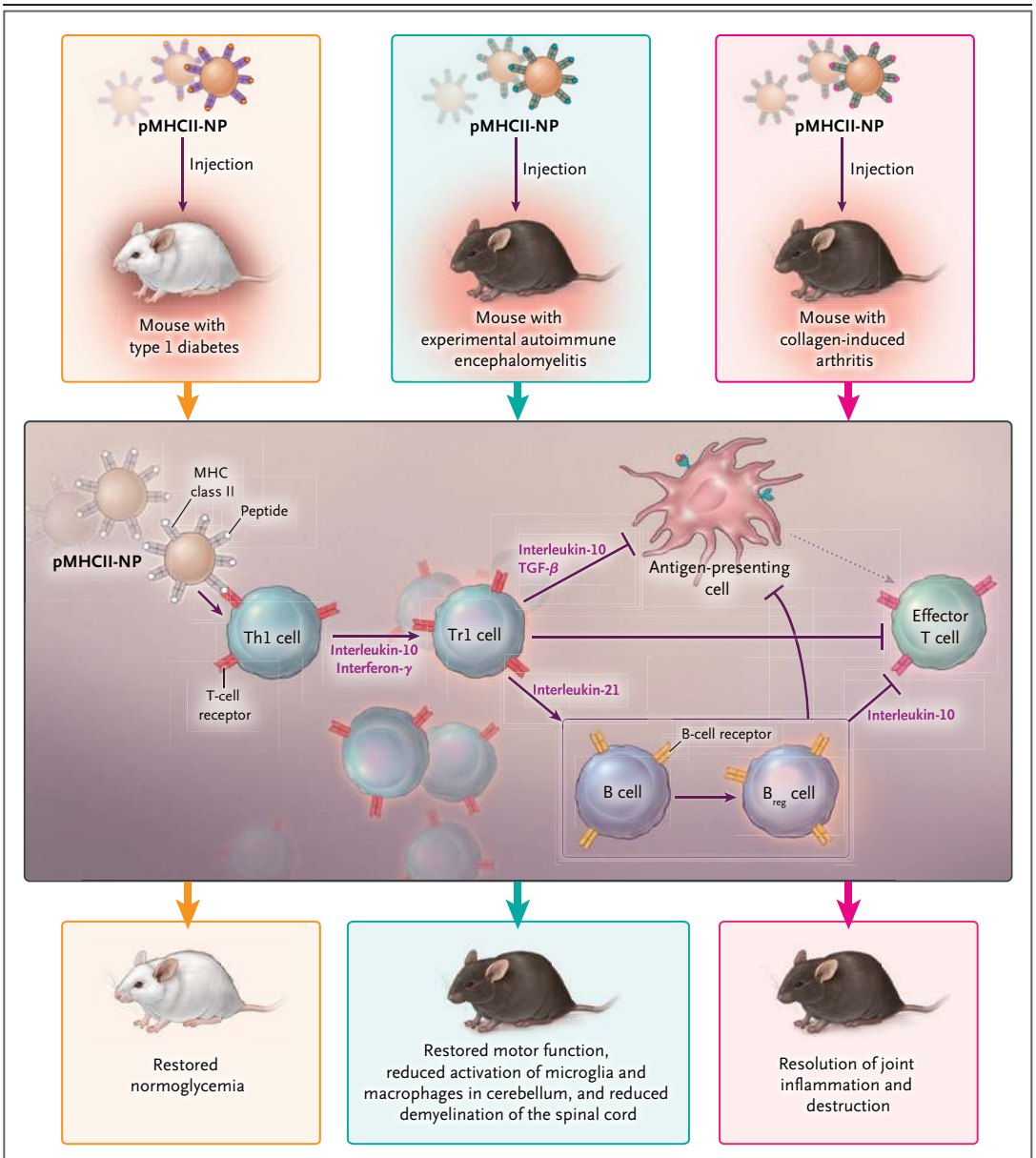

Figure 1. Teasing Out the Tr1 Cell.

Nanoparticles coated with autoimmune disease–relevant peptide bound to major histocompatibility complex (MHC) class II molecules (pMHCII-NPs) expand antigen-specific type 1 T regulatory cells (Tr1 cells) in vivo and exert therapeutic benefits in models of autoimmune disease. Santamaria and colleagues[2] injected pMHCII-NPs into mice with type 1 diabetes, experimental autoimmune encephalomyelitis, or collagen-induced arthritis. They found that systemic injection of pMHCII-NPs restored normoglycemia in diabetic mice; restored motor function, reduced activation of microglia and macrophages in the cerebellum, and reduced demyelination of the spinal cord in mice with experimental autoimmune encephalomyelitis; and resolved joint inflammation and destruction in arthritic mice. Mechanistically, pMHCII-NPs induced the generation and expansion of Tr1 cells from antigen-experienced memory T helper type 1 (Th1) cells, through an interferon-γ–dependent and interleukin-10–dependent mechanism. These Tr1 cells enhanced interleukin-10–producing regulatory B cell (B_{REG}) populations in an interleukin-21–dependent manner that exerted beneficial effects in synergy with pMHCII-NPs-expanded Tr1 cells. Tr1 cells also modulated antigen-presenting cell–mediated activation of effector T cells.

gized with that of pMHCII-NPs-expanded Tr1 cells.

Would pMHCII-NP–mediated Tr1 expansion impair systemic immunity? The authors found that only CD11b+ cells in the lymph nodes that drained affected organs — but not those in distant lymph nodes — produced lower amounts of inflammatory mediators on stimulation. (CD11b is a marker of innate immune cells.) Also, regulatory B cells were enriched only in relevant draining lymph nodes and not in other lymph nodes and spleen. As for immunity against alloantigens, mice administered pMHCII-NPs cleared acute vaccinia viral infection and mounted antibodies to another exogenous antigen as efficiently as did untreated mice.

Santamaria and colleagues went on to show that pMHCII-NPs can effect the suppression of autoimmunity in humanized mouse models of type 1 diabetes, which they generated by injecting peripheral-blood mononuclear cells (PBMCs) obtained from patients with recent-onset type 1 diabetes into immunodeficient, nonobese diabetic mice. They found that human type 1 diabetes–relevant pMHCII-NPs expand cognate Tr1-like cells and regulatory B cells from human PBMCs, an observation that represents an initial step toward the translation of this approach to the treatment of autoimmune disease in humans.

Does this study change the landscape of treatment for autoimmune diseases? No. The results are preclinical, but they do form a foundation for translational work. Currently, several approaches are being used in the clinic to target FOXP3+ regulatory T cells or Tr1 cells.[1,3,4] These approaches, however, target a polyclonal regulatory T-cell population, invoking the specter of immunosuppression and thus of a predisposition to infection and cancer. Because pMHCII-NPs "switch on" Tr1 cells in an antigen-specific manner, they seem comparatively well suited to dialing down pathogenic autoimmunity without compromising systemic immunity.

Long-term safety is a substantive concern, especially because a durable, protective effect would probably depend on continuous exposure of autoantigen-specific Tr1 cells to pMHCII-NPs. In addition, more data are required on the biodistribution and pharmacokinetics of pMHCII-NPs and their uptake and clearance by human phagocytic cells. The use of iron oxide nanoparticles in the clinic[5] for diagnostic purposes provides potential support for the clinical safety of this part of the system; whether pMHCII-NPs are safe, however, is a question that only clinical investigation can answer.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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