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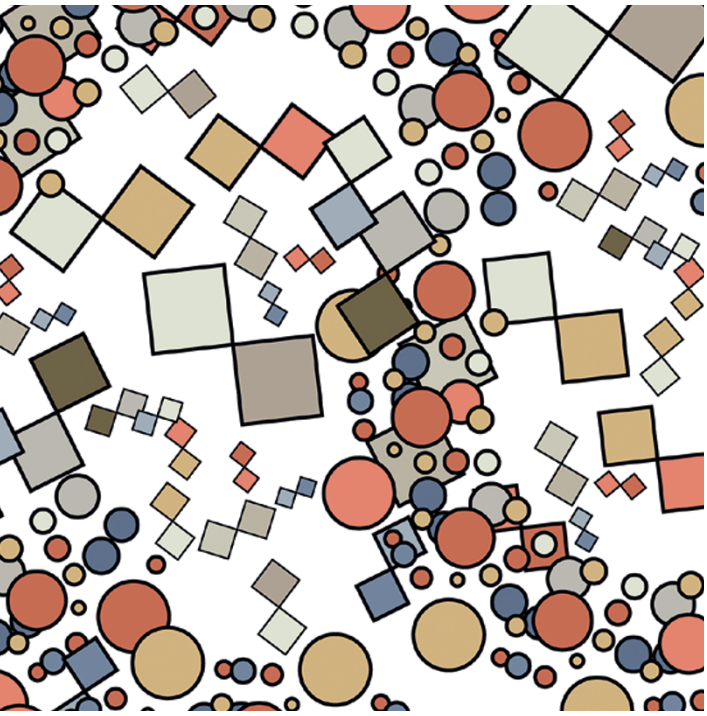
AUTOIMMUNITY

Nanoparticles engineered for antigen-specific immunotherapy

Current therapeutics for autoimmune conditions are usually nonspecific and induce general immune suppression. Now, reporting in *Nature*, Clemente-Cesares and colleagues show that nanoparticles coated with autoimmune-disease relevant peptides bound to MHC class II (pMHC-NPs) can induce antigen-specific T cells with regulatory function *in vivo*. This approach led to suppression of disease in mouse models of rheumatoid arthritis (RA), type 1 diabetes (T1D) and multiple sclerosis (MS), without affecting general immunity.

Autoimmune disease results from chronic T cell and B cell responses to autoantigens. Central to this process are autoantigen-responsive $CD4^+$ T helper (T_H) cells,

> pMHC-NPs promote the differentiation of rare pre-activated autoreactive $CD4^+$ T cells into TR1-like cells



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which orchestrate the function of other immune cells. Conversely, $CD4^+$ T cells with regulatory function (T_{Reg} cells), including $FOXP3^+CD4^+CD25^+$ T_{Reg} cells and $FOXP3^-CD4^+CD25^-$ T_R1 cells, can dampen the inflammatory process.

Based on the hypothesis that chronic autoantigen exposure may convert autoreactive T cells into regulatory T cells in a negative feedback loop, the authors engineered nanoparticles coated with the pMHC complex 2.5mi/IA^{g7}, which is a known antigenic target in the development of T1D in non-obese diabetic (NOD) mice. After intravenous injection with these pMHC-NPs twice weekly for 5 weeks, the animals developed antigen-specific $CD4^+$ T cells of the memory-like ($CD44^{hi}CD62L^{low}$) $FOXP3^-$ T_R1-like phenotype and reverted to stable normoglycaemia. Similar results were achieved when the nanoparticles were coated with pMHC complexes that contained sub-dominant (non-disease causing) NOD-specific autoantigenic peptides — but uncoated nanoparticles, pMHC monomers, peptides, peptide-coated nanoparticles or peptide-coated microparticles had no effect.

A similar strategy was used to reverse paralysis in mice with autoimmune encephalomyelitis (EAE; a model of MS) and to reduce joint inflammation in collagen-induced arthritis (CIA; a model of RA). The effect was strictly dependent on the presence of the disease-specific autoantigen–MHC complex — that is, the nanoparticles that were effective in the EAE model had no effect in the CIA model, and vice versa. However, disease-specific autoantigens besides the ones used to induce disease had therapeutic activity, indicating that the therapeutic effects of pMHC-NPs are disease-specific but dissociated from the pathogenic role of the antigenic epitope that is presented.

Further *in vitro* and adoptive transfer experiments indicated that pMHC-NPs promote the differentiation of rare pre-activated autoreactive $CD4^+$ T cells into T_R1-like cells, followed by their systemic expansion. The T_R1-like cells suppressed autoreactive helper and cytotoxic T cells through the secretion of interleukin-10 (IL-10), transforming growth factor-β (TGFβ) and IL-21. Moreover, T_R1-like cells induced the formation and expansion of regulatory B cells and downregulated the production of pro-inflammatory mediators by antigen-presenting cells. Importantly, this did not impair general immunity, as pMHC-NP-treated mice cleared acute viral infections as efficiently as untreated mice. The potential translatability of the approach to human disease was demonstrated by using human T1D-relevant pMHC-NPs in NOD severe combined immunodeficient *Il2rg*$^{-/-}$ mice reconstituted with peripheral blood mononuclear cells from T1D patients.

The authors suggest that pMHC-NPs may form a new class of therapeutics capable of resolving complex autoimmune disease in a disease- and organ-specific manner, without compromising systemic immunity.

Alexandra Flemming

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