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NANOMEDICINE

Design and conquer

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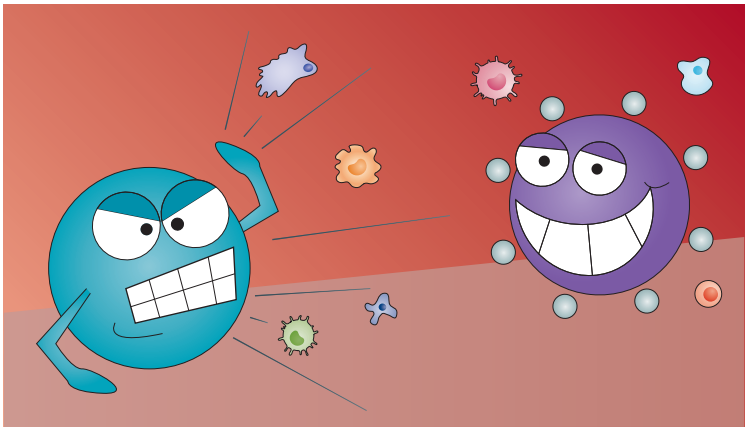
A new class of nanomaterials with unique surface properties can resolve autoimmune inflammation, without compromising the general immune system, report Yang Yang, Pere Santamaria and colleagues in *Nature Nanotechnology*.

Nanoparticles decorated with proteins that are associated with specific autoimmune diseases, such as rheumatoid arthritis, have previously been used as platforms to amplify disease-suppressing regulatory T cells, thereby resolving inflammation. However, the translation of these nanomedicines for immunotherapy from bench to bedside has proven challenging owing to a lack of detailed examination of potential toxicity, and of the physicochemical and cell-binding properties that are directly responsible for biological and therapeutic activity. To overcome these challenges, the researchers carried out an extensive analysis of the key synthesis variables, modes of cell binding and receptor targeting, biodistribution, pharmacokinetics and toxicology, using a broad range of *in vitro* and *in vivo* models.

By experimenting with iron oxide nanoparticles coated with increasing numbers of protein complexes displaying autoimmune disease-associated peptides, the researchers discovered that the ability of these compounds to reprogramme effector and memory T cells into regulatory T cells is a direct function of molecular density (that is, space separating individual molecular complexes on the nanoparticle surface). Importantly, they discovered the existence of unexpected protein density thresholds for agonistic activity. They further observed that the ability of these compounds to expand the reprogrammed regulatory T cells is dose-dependent. Thus, the two key biological activities of these novel compounds, T cell reprogramming and regulatory T cell expansion, are controlled by different variables. "We defined the fundamental engineering principles and mechanisms that enable this new class of drugs to 'reprogramme' disease-causing white blood cells into their disease-suppressing counterparts," explains Santamaria.

To further elucidate the roles of the various physicochemical properties of these compounds on biological activity, the team investigated the kinetics and geometry of their interactions with immune cells. They observed that binding to cognate T cells (carrying antigen receptors specific for the coated protein complexes) rapidly triggers the assembly of large clusters of nanoparticles on the cell membrane, leading to the sustained ligation of the T cells' antigen receptors that are responsible for T cell reprogramming. Remarkably, the ability of these compounds to trigger the formation of these nanoparticle clusters, which is essential for biological activity, only occurred when the molecular density of the coating was at or above the threshold value. Furthermore, these observations also occurred when using nanoparticles decorated with human autoimmune disease-relevant proteins and human patient-derived immune cells. In addition, the authors demonstrated that these nanoparticle–protein complexes have short half-lives *in vivo*, do not accumulate in any of the organs studied, and do not have any appreciable toxicity in mice or off-target effects in a zebrafish embryo screen.

These new insights into the role of nanoparticle–protein complex density in driving T cell triggering and cellular reprogramming creates new opportunities in the design of targeted nanomedicines. The authors plan to harness these findings to develop more advanced immunotherapeutics with a view to clinical translation. "We are advancing these complexes to the clinic for the treatment of specific autoimmune diseases," concludes Santamaria.



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ORIGINAL ARTICLE Singha, S. *et al.* Peptide-MHC-based nanomedicines for autoimmunity function as T-cell receptor microclustering devices. *Nat. Nanotechnol.* http://dx.doi.org/10.1038/nnano.2017.56 (2017)
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