NETs generate structured antimicrobial peptide-nucleosome immune complexes with inter-DNA spacings optimal for TLR9 activation

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Interleukin 33 (IL-33), initially described as an alarm released by cells following cell damage, can also act immunosuppressive by inducing regulatory T cells (Treg). Disruption of IL-33 by using IL-33-specific siRNA markedly decreases the number of CD4+ T cells in the wild-type mice, whereas IL-33 increased the number of Treg. IL-33 decreased the number of Treg in the skin and serum of psoriatic patients. On the other hand, in experimental autoimmune encephalomyelitis in rats, Treg are implicated in the pathogenesis of the disease. Treg are impaired in their response to IL-33 in the imiquimod (IMQ)-induced psoriasis-like model. IL-33 was enhanced in skin and serum of IMQ-mice. To study the influence of IL-33, Treg was transferred into naive mice which were sensitized with the antigen and challenged with the antigen. Our results suggest that IL-33 can be used as a strategy to improve the function of Treg in psoriasis.

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Immunization of dermatomyositis-specific autoantigen transcripational intermediary factor (TFI)-γ induces experimental myositis in mice

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The mechanisms that govern the pathogenesis of psoriasis is characterized by part by breakdown of immune tolerance to self-DNA. Recent work demonstrates that the human antimicrobial peptide (AMP) LL-37 overexpressed in psoriasis organizes naked DNA into periodic nanocrystals to potentially activate Toll-like receptor 9 (TLR9) in plasmacytoid dendritic cells (pDCs). Interestingly, a sub-set of self-DNA in psoriatic lesions remains bound to histones. Like DNA nucleosome core particles (NCPS) released from neutrophil extracellular traps (NETs). At present, it is unknown how NET components like AMPs interact with NCPS, and whether AMP-NCPS complexes form structures compatible with TLR9 activation in psoriasis. Here, we combine synchronization X-ray scattering, cryo-electron microscopy, and computer simulations to demonstrate that under a broad range of conditions, NCPS stack to columns that present periodically arranged diDNA ligands like threads on a screw, allowing for optimal interfibrillation with clusters of TLR9. Remarkably, simulations and electron microscopy indicate that the superhelical pitch of DNA wrapped around the NCPS column relaxes to a value that is well-matched with the steric size of TLR9, which predicts strong immune activation. Taken together, our results suggest that AMPs can remodel the self-DNA into structural elements that are similar to NETs into potent allergens of inflammation. Preliminary immune activation experiments will be presented.

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Langerhans cells suppress CD8 T cells in situ during acute graft-versus-host disease-like autoimmune mucocutaneous disease

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Previous studies revealed that cutaneous manifestations of acute graft-versus-host disease-like autoimmune mucocutaneous disease patients, who donate immune cells react against host tissues after allologeneic hematopoietic stem cell transplant, are mediated by CD8 T cells. Cutaneous aGVHD is histologically characterized by reduced number of epidermal Langerhans cells (LCs). To investigate the roles of LCs, we analyzed a murine model using transgenic mice that express membrane-bound chicken ovalbumin under control of a keratin 14 promoter (K14-mOVA Tg). CD8 T cells which develop aGVHD-like mucocutaneous disease after OVA-specific CD8 T cell (OT-I) transfer. LCs did not disappear from the epidermis in this model, unlike in aGVHD induced by major histocompatibility complex (MHC)-mismatched bone marrow (BM) transplantation which develop aGVHD-like mucocutaneous disease after OVA-specific CD8 T cell (OT-I) transfer. LCs decreased after TFI-γ immunizations with no injury compared to wild-type mice. Collectively, TFI-γ is an autoregulator with essential immunogenicity to induce experimental myositis, in which the muscle injury is directly mediated by CD8+ T cells, but not CD4+ T cells or antibodies. TFI-γ-induced experimental myositis would be a useful tool to investigate pathology of TFI-γ antibody-associated dermatomyositis.