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AUTOIMMUNITY

DNASE1L3 prevents anti-DNA responses

> DNASE1L3 secreted by haematopoietic cells represses autoreactivity

Deoxyribonuclease-γ (DNASE1L3) could be developed for therapeutic purposes in systemic lupus erythematosus (SLE), a new study suggests. "We identified microparticle-associated chromatin as an important self-antigen that may drive loss of tolerance in SLE, and circulating DNASE1L3 as an important regulatory enzyme that prevents SLE development by digesting this chromatin," reports Vanja Sisirak, lead author of the *Cell* paper presenting these data. "These findings may pave the way for new therapeutic strategies that aim at restoring DNASE1L3 function to prevent SLE development."

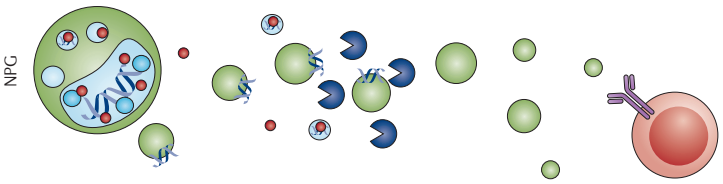
Previous studies had linked *DNASE1L3* null mutations and hypomorphic variants with susceptibility to inherited and sporadic forms of SLE. To determine the mechanisms underlying these associations, Sisirak and colleagues developed a novel monogenic mouse model, in which knockout of the *Dnase1l3* gene recapitulates the cardinal features of human SLE. "This model can be used to dissect mechanisms that lead to the break of tolerance to self-DNA involved in SLE pathogenesis," says Sisirak.

The investigators found that *Dnase1l3*-deficient mice rapidly developed antibodies to double-stranded DNA and chromatin, followed later by immune activation, IgG deposition in the kidney glomeruli and glomerulonephritis. This autoreactivity did not require the cytosolic DNA sensor STING (stimulator of interferon genes), whereas MyD88, which transduces Toll-like receptor and IL-1 receptor signals, was essential, suggesting DNASE1L3 does not target intracellular DNA.

Transfer of bone marrow cells from DNASE1L3-deficient mice into wild-type animals led to a progressive loss of circulating DNASE1L3 activity that correlated with the occurrence of SLE features, indicating that serum DNASE1L3 secreted by haematopoietic cells (primarily macrophages and dendritic cells) represses autoreactivity. "We then uncovered one apparent mechanism of action of DNASE1L3, which is to digest chromatin in microparticles released from apoptotic cells," explains Sisirak. "This specific activity was supported by the observation that DNASE1L3-deficient mice and humans have elevated DNA levels in the plasma, particularly in their circulating microparticles." These microparticles are targeted by autoantibodies present in the sera of DNASE1L3-deficient mice and humans, and from patients with sporadic SLE, but treatment of microparticles with exogenous DNASE1L3 abrogated antibody binding.

Sarah Onuora

ORIGINAL ARTICLE Sisirak, V. *et al.* Digestion of chromatin in apoptotic cell microparticles prevents autoimmunity. *Cell* http://dx.doi.org/10.1016/j.cell.2016.05.034 (2016)



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