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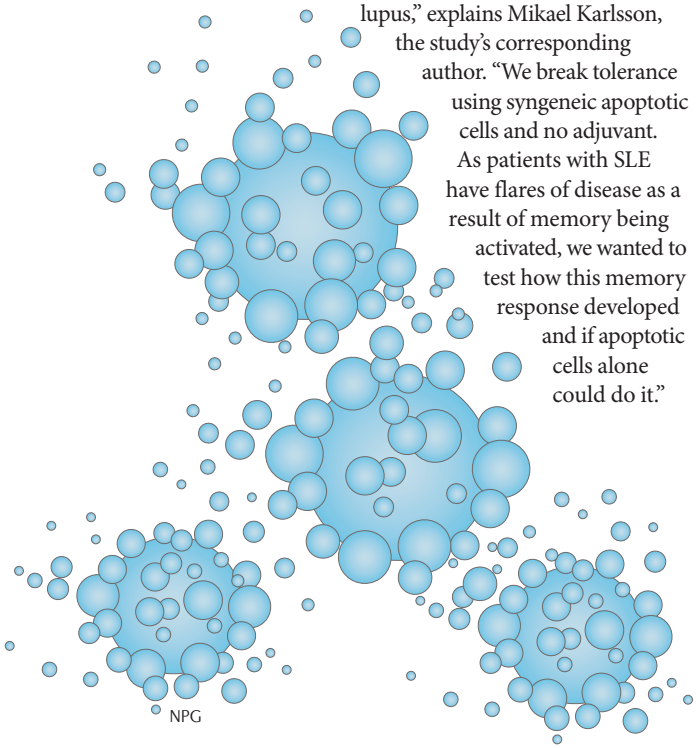
AUTOIMMUNITY

Apoptotic cells induce immune memory

> A second booster dose of apoptotic cells led to ANA positivity and deposition of immune complexes in the kidneys

A new study reported in *The Journal of Immunology* shows that autoantigens derived from apoptotic cells are sufficient to induce a break of immune tolerance in wild-type mice, and that repeated exposure to these autoantigens leads to an autoreactive memory response associated with lupus-like pathology. The findings provide new insights into how self-memory contributes to the development of systemic lupus erythematosus (SLE) and could have implications for the treatment of this disease.

"We have been studying the response to self-antigens for a while, with a focus on B-cell tolerance, and we were interested in just how much relevance the model we used had for lupus," explains Mikael Karlsson, the study's corresponding author. "We break tolerance using syngeneic apoptotic cells and no adjuvant. As patients with SLE have flares of disease as a result of memory being activated, we wanted to test how this memory response developed and if apoptotic cells alone could do it."



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In wild-type mice, injection of apoptotic cells weekly for 5 weeks induced a transient increase in serum levels of anti-DNA and anti-phosphorylcholine IgG, but neither antinuclear antibody (ANA) positivity nor kidney pathology was observed. Following resolution of this initial response, re-exposure to the autoantigens by administration of a single booster injection of apoptotic cells induced a rapid autoimmune response. A second booster dose of apoptotic cells led to ANA positivity and deposition of immune complexes in the kidneys of the mice as well as changes in the glomerular tissue architecture, with evidence of hypertrophy and mesangial thickening.

The response to the booster injections was characterized by IgG subclass switching and increased frequencies of germinal centre B cells and T follicular helper cells, although no sign of affinity maturation to phosphorylcholine was detected. "That there indeed is a memory response to self-antigens is in itself a very significant and novel finding," reports Karlsson. "It was also interesting to see that this memory response in many regards behaves like a classical memory response but with some important differences, such as a lack of affinity maturation."

Notably, the autoreactive memory response was transferable: following transfer of splenocytes from donor mice that had been injected with apoptotic cells weekly for 4 weeks and upon re-exposure to apoptotic cells, irradiated recipient wild-type mice showed rapid production of subclass-switched IgG autoantibodies and their spleens showed development of extrafollicular foci.

Moreover, microarray analysis demonstrated that the memory response to apoptotic-cell-derived autoantigens was associated with particular autoantibody specificities. Additional experiments led the researchers to speculate that increased IgG class-switching in the memory response could contribute to the increased response to apoptotic cells via FcγR-mediated mechanisms.

"Using this immunization model we recalled the primary response not just once, but twice, which allowed us to discover that the second memory response was more pathogenic," Karlsson explains. "This finding shows an important similarity with the way so-called flares in SLE are provoked and therefore could have implications for the treatment of this disease and also for understanding how SLE progresses."

Taking this work forward, the researchers plan to investigate how different parts of the innate immune system are involved in shaping the memory response to apoptotic-cell-derived antigens, with a particular focus on the different innate sensor systems that recognize these antigens. "Our new model also provides a way to test how different treatments affect memory to self antigens," Karlsson suggests.

Sarah Onuora

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