AUTOIMMUNITY ENGINEERED AICDA BALANCES B CELLS

Selectively targeting the function of activation-induced cytidine deaminase (AICDA) could reduce the production of autoantibodies in systemic lupus erythematosus (SLE), suggest data from a new study in mice. John Mountz and colleagues analyzed the effect of expressing a mutated *Aicda* transgene in BXD2 mice, which suffer several symptoms of rheumatic disease.

AICDA is needed for two B-cell germinal center (GC) processes, somatic hypermutation (SHM) and class switch recombination (CSR), that produce high affinity autoantibodies. Raised expression of *Aicda* in the spleens of BXD2 mice causes large GCs to form there and produce autoantibodies. In a seeming paradox, however, knockout of *Aicda* in normal mice causes large GCs to form in response to antigens. *Aicda*'s CSR role induces double-strand breaks (DSB) in immunoglobulin genes, thus, in its absence, B cells escape DNA damage-induced apoptosis after initiation of a GC reaction, resulting in enlarged GCs. So why does excess *Aicda* cause GC enlargement in the BXD2 mice, and could normalization of its activity reduce disease burden?

To find out, Mountz *et al.* studied BXD2-*Aicda*-DN mice, which express a dominant-negative *Aicda* transgene that carries a mutation shown to affect the SHM function of the enzyme without reducing the frequency of DSB. At one year >90% of BXD2-*Aicda*-DN mice survived, compared with 50% of BXD2 mice, and they developed fewer disease symptoms. Analysis of the spleens showed that transgene expression enhanced GC apoptosis, and reduced B-cell proliferation and GC response.

Specific targeting of AICDA's SHM function might be a future strategy for therapy in SLE. "It will be difficult to find a specific inhibitor," says Mountz, "but we have developed a high throughput screening assay."

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Original article Hsu, H.-C. *et al.* Inhibition of the catalytic function of activation-induced cytidine deaminase (AICDA) promotes apoptosis of germinal center B cells. *Arthritis Rheum.* doi:10.1002/art.30257