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EXPERIMENTAL ARTHRITIS

Mobilizing killer cells to combat CIA

"Blockade of the NKG2A inhibitory receptor on NK cells 'releases the brakes' in these cells and allows them to destroy arthrogenic T cells without the risk of untoward side effects associated with antibodies specific for activating receptors," says Harvey Cantor. Now published in *Proceedings of the National Academy of Sciences*, the data Cantor describes show that enhancing the activity of natural killer (NK) cells to destroy activated autoimmune T cells arrests the progression of collagen-induced arthritis (CIA), and could be a new approach to tackle rheumatoid arthritis.

> "...injection of anti-NKG2A antibody ... reduced numbers of T_{FH} and T_H17 cells, but not T_H1 or T_H2 cells..."

"Current antibody-based approaches to deplete pathogenic T cells use antibodies directed at activating receptors on T cells," continues Cantor. "Many of these antibodies can partially stimulate T cells, resulting in activation-induced untoward side effects, including 'cytokine storms'." Key to avoiding such problems is defining which T helper (T_H) lineages are aberrantly activated in disease, and finding ways to target them specifically. To identify the T_H cells that mediate CIA pathogenesis, Cantor and colleagues transferred various collagen-reactive T_H cell subsets and B cells into mice deficient in NK cells, and examined the resultant joint pathology. Interaction of follicular T_H (T_{FH}) cell-dependent autoantibody production with proinflammatory actions of type 17 T_H (T_H17) cells was thereby implicated in the disease process. Noting that transfer of activated immune cells failed to elicit disease in NK-cell-sufficient mice, and having found previously that blocking the inhibitory signal delivered by the NKG2A receptor, as Cantor puts it, "unleashes NK cell killing of activated, autoreactive T cells," (see further reading), the researchers hypothesized that enhancing NK cell activity through use of an anti-NKG2A antibody might be a new therapeutic approach for rheumatoid arthritis. Indeed, injection of the antibody into collagen-immunized mice reduced numbers of T_{FH} and T_H17 cells, but not T_H1 or T_H2 cells, and ameliorated disease.

"The advantage of this approach over current strategies is that it depends on directed lysis of a small subpopulation of autoreactive T cells, rather than a general effect on the T cell repertoire," says Cantor. He adds that NKG2A is conserved between mice and humans, and anti-NKG2A therapy has entered clinical trials.

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Original article Leavenworth, J. W. *et al*. Mobilization of natural killer cells inhibits development of collagen-induced arthritis. *Proc. Natl Acad. Sci. USA* **108**, 14584–14589 (2011)

Further reading Lu, L. *et al*. Regulation of activated CD4$^+$ T cells by NK cells via the Qa-1-NKG2A inhibitory pathway. *Immunity* **26**, 593–604 (2007)