CONNECTIVE TISSUE DISEASES

An inside job on T-cell signaling in SLE—
dipyridamole blocks expression of key molecules

A drug already in clinical use as a vasodilator and inhibitor of platelet activation could be a new therapy for systemic lupus erythematosus (SLE), if data from studies in mice and in human cells can be borne out in clinical trials. “We believe that dipyridamole will prove to serve patients with SLE as an adjunct to current treatment approaches. In fact, administering dipyridamole may permit reduced doses of prednisone and reduction of side effects,” says George Tsokos, lead author of a paper reporting the new data in *Arthritis & Rheumatism*.

T cells drive SLE pathogenesis by helping B cells to produce pathogenic autoantibodies, and by producing proinflammatory cytokines, after infiltrating the tissues that are affected by the disease, such as skin and kidneys. Key to the inappropriate and sustained activation of B cells by T cells in SLE is the ligand for CD40 (CD40L), which is overexpressed by T cells in SLE and is an obvious target for therapy. Nevertheless, “anti-CD40L therapy was discontinued because it was complicated by thrombosis caused by platelet activation and aggregation, as platelets also express CD40L,” explains Syamal K. Datta of Northwestern University, Chicago. In using dipyridamole, he continues, “the authors have found a way to reduce CD40L hyperexpression.” Besides this effect, the drug also inhibited the production of cytokines including IL-6, IL-17 and interferon γ , and disrupted T-cell-dependent antibody production by B cells, in the MRL/*lpr* mouse model of SLE and in cells from human patients. Furthermore, treatment with dipyridamole delayed the progression of nephritis in the MRL/*lpr* mice, and after a 3-week course abrogated the 60% death rate observed in animals that received control treatment.

So, what is this relatively cheap, tried-and-tested drug doing in SLE cells to elicit such promising data? The inspiration to try it came from two converging

strands of research: study of the role of the transcription factor nuclear factor of activated T cells (NFAT) in SLE, and work aimed at blocking the calcineurin–NFAT signaling pathway. “T cells from patients with active SLE exhibit at least a twofold increase in nuclear NFAT when compared with control T cells,” notes Tsokos. This increase results from another characteristic of SLE T cells—a strong and early influx of calcium after activation (in comparison with normal T cells), which increases calcineurin-dependent activation, and nuclear translocation, of NFAT. Nuclear NFAT activates the transcription of CD40L. “Dipyridamole was recently found to inhibit NFAT interactions without affecting global calcineurin phosphatase activity,” says Tsokos, explaining that this specificity means that patients using dipyridamole should escape some of the toxicity associated with the calcineurin inhibitors tacrolimus and ciclosporin, two potent immunosuppressive drugs both associated with severe adverse events.

Exploring the implications of these previous discoveries for SLE, the researchers found that CD3⁺CD4⁺CD8[−] T cells and CD4⁺ T cells from MRL/*lpr* mice had a high calcium influx even before disease symptoms started, and that NFAT gradually accumulated in the cells with age. In co-culture with B cells, these T cells

induced immunoglobulin production in a calcineurin-dependent manner.

“Although other biologics to block CD40 signaling are in development, they are not at hand and might be more expensive,” says Datta, adding that the known platelet-inhibiting effect of dipyridamole might offer a second benefit in SLE, as platelets contribute to SLE pathogenesis. He cautions, however, that some questions remain. Production of IL-2, which is already deficient in SLE, was further inhibited by dipyridamole, suggesting that the drug would be useful for suppressing flares of active disease but not as long-term therapy. Also, notes Datta, alterations in the T-cell populations, reported but not discussed in the paper, might signify an effect of dipyridamole on other cell types.

Given that NFAT partners with different factors in different T-cell subtypes, “the exact timing and dose of NFAT inhibition would be key,” says Tsokos, and should be tested in preclinical studies, “to ensure that autoimmune processes are abrogated without inhibiting counter-inflammatory regulation.”

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