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CONNECTIVE TISSUE DISEASES

IS APRIL FOOLING US ALL IN SLE?

In 2011, belimumab, an anti-BAFF antibody, was approved for the treatment of systemic lupus erythematosus (SLE). APRIL, a cytokine closely related to BAFF, is also a potential therapeutic target in SLE. However, "direct evidence either in support of or against a role for APRIL per se in SLE had never been reported," says William Stohl, of the University of Southern California, Los Angeles. Now, Stohl and collaborators have presented data that increase our knowledge of APRIL's influence on SLE pathogenesis.

In contrast to Stohl and co-workers' previous findings in *Baff*$^{-/-}$ mice, their new data reveal that APRIL deficiency in SLE-prone NZM 2328 mice offers no protection against, and might even slightly exacerbate, development of the disease. The authors speculate that any worsening of disease might be explained by decreased heterotrimerization of BAFF and APRIL in *April*$^{-/-}$ mice, which could promote formation of more potently signal-promoting BAFF homotrimers. "We can use APRIL-deficient mice as a starting point to elucidate the critical BAFF–BAFF receptor interactions in SLE without any potentially confounding effects from APRIL," suggests Stohl. "This could ultimately lead to more selective therapeutic targeting within the greater 'BAFF axis' and greater therapeutic benefit," he continues.

Additional data from this study revealed that BAFF and APRIL doubly-deficient mice had reduced bone marrow plasma cells and antibody titers compared with both wild-type and *Baff*$^{-/-}$ mice. However, "mice doubly-deficient in BAFF and APRIL develop renal immunopathology to the same mild degree as do mice singly-deficient in BAFF," states Stohl. "In the NZM 2328 mouse model, there is no advantage to eliminating both BAFF and APRIL in comparison to eliminating BAFF alone."

"It must be stressed that our findings are limited to NZM 2328 mice," explains Stohl. "Findings in mice may not fully translate to humans, and studies in genetically-deficient hosts may not fully reflect outcomes in hosts treated with pharmacologic neutralizing agents." Nevertheless, these new insights raise concerns regarding the therapeutic targeting of APRIL in SLE; only time will tell whether these worries are well founded.

David Killock

Original article Jacob, C. O. *et al*. Dispensability of APRIL to development of systemic lupus erythematosus in NZM 2328 mice. *Arthritis Rheum.* doi:10.1002/art.33458.