IN BRIEF

AUTOIMMUNITY

Novel autoantibody in Sjögren syndrome

A novel autoantigen, calponin-3, was identified in the serum of a patient with Sjögren syndrome (SS) by mass spectrometry peptide sequencing. Anti-calponin-3 antibodies were then detected in patients with SS (11% of patients), systemic lupus erythematosus (8.7%), myositis (5.1%) and multiple sclerosis (6.8%). In patients with SS, the frequency of these antibodies was highest in those with neuropathies. Calponin-3 was expressed in perineuronal satellite cells.

ORIGINAL ARTICLE Birnbaum, J. et al. Anti-calponin-3 autoantibodies: a new specificity in patients with Sjögren's syndrome. ***Arthritis Rheum.*** https://doi.org/10.1002/art.40550 (2018)

LUPUS NEPHRITIS

Changing patterns of lupus nephritis over five decades

Moroni and colleagues analysed clinical and histological data from 499 patients with lupus nephritis (LN) diagnosed between 1970 and 2016. The researchers detected an increase in patient age at time of diagnosis over this time period as well as an increase in time between onset of systemic lupus erythematosus and diagnosis of LN. Survival without end-stage renal disease also significantly increased ($P = 0.0019$).

ORIGINAL ARTICLE Moroni, G. et al. Changing patterns in clinical–histological presentation and renal outcome over the last five decades in a cohort of 499 patients with lupus nephritis. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2017-212732 (2018)

INFLAMMATION

Validating canakinumab therapy for autoinflammation

Patients with colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency or tumor necrosis factor receptor-associated periodic syndrome (TRAPS), which are monogenic autoinflammatory diseases characterized by recurrent fever flares, were randomly assigned to receive canakinumab or placebo at the time of a flare and every 4 weeks thereafter. Patients who received canakinumab were significantly more likely to experience resolution of the flare and no further flare until week 16. The most frequently reported adverse events with canakinumab treatment were infections, with few being serious.

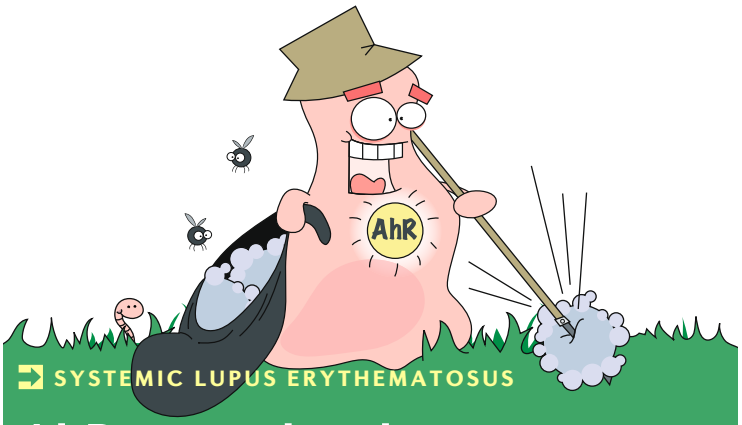
ORIGINAL ARTICLE De Benedetti, F. et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N. Engl. J. Med.* **378**, 1908–1919 (2018)

RHEUMATOID ARTHRITIS

Tocilizumab or TNF inhibitors in RA?

Lauper and colleagues investigated the efficacy of tocilizumab and TNF inhibitors as monotherapy or in combination with DMARDs in patients with rheumatoid arthritis who had previously received at least one biologic DMARD. Drug retention was found to be longer with tocilizumab monotherapy and combination therapy than with TNF inhibitor therapy. Clinical disease activity scores and low disease activity rates were comparable between groups. The researchers conclude that tocilizumab is a reasonable therapeutic option in patients with inadequate response to biologic DMARDs.

ORIGINAL ARTICLE Lauper, K. et al. Comparative effectiveness of tocilizumab versus TNF inhibitors as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis after the use of at least one biologic disease-modifying antirheunmatic drug: analyses from the pan-European TOCERRA register collaboration. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2017-212845 (2018)



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SYSTEMIC LUPUS ERYTHEMATOSUS

AhR controls tolerance to cell debris

Impaired recognition and clearance of cellular debris are important factors in the pathogenesis of systemic lupus erythematosus (SLE). A new study sheds light on the mechanisms involved in regulating immune tolerance to cell debris and suggests an important role for the transcription factor aryl hydrocarbon receptor (AhR).

"Cell death can have a profound impact on immunity," states corresponding author Tracy McGaha. "When cells become apoptotic they can drive immune-suppressive mechanisms that prevent immune reactivity against dying cell-associated antigens. This process is believed to be a key mechanism in the prevention of autoimmunity."

By studying changes in genes expression patterns in murine phagocytes upon in vitro co-culture with apoptotic cells, the researchers identified AhR-responsive genes that were upregulated following exposure to cell debris. High-throughput sequencing and chromatin analysis revealed that AhR specifically interacted with promoters to upregulate genes encoding regulatory cytokines such as IL-10.

These changes in gene activity caused a shift towards an immunoregulatory phenotype in phagocytes exposed to apoptotic cell debris. Importantly, blocking AhR caused a reduction in IL-10 production and a shift towards the production of pro-inflammatory cytokines by these cells, suggesting that AhR functions as a regulator of immune tolerance by suppressing inflammatory responses to cell debris.

Anti-nuclear antibodies are a key feature of SLE, and previous studies have shown that DNA can be exposed on cell debris. Using bone marrow-derived macrophages from *Tlr9*-deficient mice, McGaha and colleagues revealed how the recognition of DNA from apoptotic cells by Toll-like receptor 9 (TLR9) can cause AhR activation and the production of IL-10. "The fact that TLR9 was driving AhR activation goes against typical mechanistic dogma regarding the role of TLRs in immunity," says McGaha. "However, it is consistent with previous observations that suggest that under certain circumstances otherwise pro-inflammatory circuits can drive regulatory immunity."

In two different mouse models of spontaneous lupus-like disease, pharmacological manipulation of AhR activity altered disease severity and progression. Blockade of AhR activity increased the severity of lupus-like disease, whereas the administration of an AhR agonist prevented disease in young mice and ameliorated disease in mice with established lupus-like disease.

Interestingly, apoptotic cells also activated AhR and induced IL-10 production in human myeloid cells, and AhR transcriptional signatures similar to those seen in lupus-prone mice were seen in myeloid cells from patients with SLE. "Targeting AhR in human disease may have a similar therapeutic effect on disease activity to that seen in mice," concludes McGaha, continuing "we are currently developing small molecule inhibitors of AhR for clinical applications."

Joanna Collison

ORIGINAL ARTICLE Shinde, R. et al. Apoptotic cell–induced AhR activity is required for immunological tolerance and suppression of systemic lupus erythematosus in mice and humans. *Nat. Immunol.* https://doi.org/10.1038/s41590-018-0107-1 (2018)