IN BRIEF

ANTIPHOSPHOLIPID SYNDROME

β2GPI–HLA-DR linked to recurrent pregnancy loss

Autoantibodies that recognize a complex of β2-glycoprotein I (β2GPI) and HLA-DR were associated with recurrent pregnancy loss in a Japanese multi-centre cross-sectional study. Of the 227 women with recurrent pregnancy loss included in the study, 52 (22.9%) were positive for anti-β2GPI–HLA-DR antibodies. By contrast, only 45 (19.8%) were positive for at least one of the five antiphospholipid antibodies (aPL) required for a classification of antiphospholipid syndrome (APS). Furthermore, of the 112 women in the study who had clinical manifestations of APS but were negative for classification criteria aPL, 21 (18.8%) were positive for anti-β2GPI–HLA-DR antibodies.

ORIGINAL ARTICLE Tanimura, K. et al. The β2-glycoprotein I/HLA-DR complex is the major autoantibody target in obstetric antiphospholipid syndrome. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41410 (2020)

RHEUMATOID ARTHRITIS

Prevotella species associated with RA-risk genes

A polygenic risk score for rheumatoid arthritis (RA), which was developed using a cohort of identical twins who did not have RA and validated against a diagnosis of RA using samples from the UK Biobank, was associated with the presence of *Prevotella* spp. in the gut in the absence of RA, suggesting an association between gut microbiota and host genotype before disease onset. The association between genes and microbiota was further validated in a cohort of first-degree relatives of patients with RA, in whom *Prevotella* spp. were associated with the *HLA-DRB1* shared epitope and with preclinical arthritis.

ORIGINAL ARTICLE Wells, P. M. et al. Associations between gut microbiota and genetic risk for rheumatoid arthritis in the absence of disease: a cross-sectional study. *Lancet Rheumatol.* **2**, E418–E427 (2020)

SPONDYLOARTHRITIS

Axial SpA with enthesitis characterized

Data on 477 patients with axial spondyloarthritis (axSpA) from the Corrona psoriatic arthritis/spondyloarthritis registry (a prospective observational cohort from the USA) have revealed links between the presence of enthesitis and poor outcomes. Patients with axSpA who had enthesitis were more likely to be female, have non-radiographic disease and have a history of depression or fibromyalgia, as well as having greater disease activity (according to several measures) and worse quality of life than patients with axSpA who did not have enthesitis.

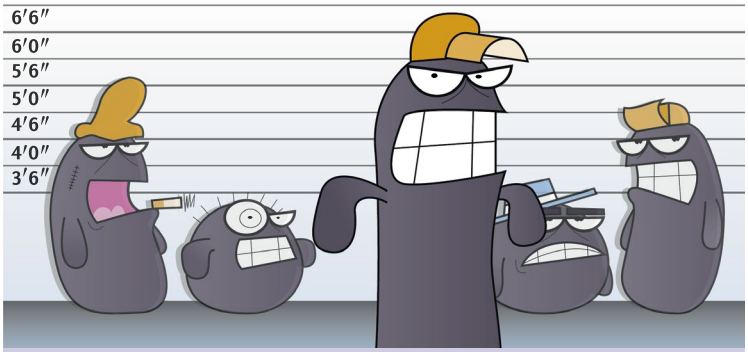
ORIGINAL ARTICLE Mease, P. J. et al. Characterization of patients with axial spondyloarthritis by enthesitis presence: data from the Corrona psoriatic arthritis/spondyloarthritis registry. *ACR Open Rheumatol.* https://doi.org/10.1002/acr2.11154 (2020)

QUALITY OF LIFE

Pain and fatigue persist in PsA despite treatment

In a study of 640 patients with psoriatic arthritis (PsA) from 13 countries, 37.7% reported severe pain and 45.6% reported severe fatigue after more than 3 months of treatment with TNF inhibitors, suggesting a need for improved disease management in PsA. Health-related quality of life and work productivity scores were worse in patients with moderate or severe pain or fatigue compared with those with low pain or fatigue. Mental health scores (self-reported happiness and the mental health domain of short form-36 v2) were also lowest in patients reporting the most severe pain or fatigue.

ORIGINAL ARTICLE Conaghan, P. G. et al. Relationship of pain and fatigue with health-related quality of life and work in patients with psoriatic arthritis on TNFi: results of a multi-national real-world study. *RMD Open* **6**, e001240 (2020)



RHEUMATOID ARTHRITIS

PRIME suspects in RA flares

Rheumatoid arthritis (RA) is characterized by recurrent flares in disease activity, yet relatively little is known about the physiological events that precede a flare. A new study published in *The New England Journal of Medicine* provides evidence for immune alterations that occur 2 weeks ahead of a flare and suggests a new cellular culprit in flare initiation.

"We were interested in understanding the molecular events that lead to flares of RA," says corresponding author Dana Orange, explaining the rationale behind the study. To investigate these molecular events, the researchers performed RNA sequencing on weekly blood samples from four patients with RA and also collected paired data on disease activity. "Given that it is unrealistic to ask patients to come to the hospital for blood draws every week, the volunteers collected their own blood at home via fingerstick and mailed the samples, along with a RAPID3 disease activity questionnaire, to the lab each week for a minimum of a year," explains Orange.

The research team identified gene expression signatures associated with myeloid cells, neutrophils and platelets during the flares themselves, and another signature associated with naive B cells in samples taken 2 weeks before a flare. Intriguingly, a gene expression signature strongly emerged in samples taken 1 week before a flare that was reminiscent of mesenchymal cells.

"We compared this mesenchymal signature to synovial single-cell RNA sequencing data, previously collected by the Accelerating Medicine Partnership, and found that the gene signature overlapped with that of synovial sublining fibroblasts, suggesting that a cell similar to a synovial fibroblast might be detectable in blood," states Orange.

Taking this theory one step further, the researchers looked for these fibroblast-like cells in blood samples from 19 additional patients with RA. The cells they detected were $CD31^{-}CD45^{-}PDPN^{+}$ and were more common in patients with RA than in healthy individuals. RNA sequencing of sorted blood $CD31^{-}CD45^{-}PDPN^{+}$ cells revealed enrichment for genes upregulated 1 week before a flare and for genes expressed in synovial fibroblasts, leading the researchers to name these cells pre-inflammatory mesenchymal (PRIME) cells.

"The discovery of PRIME cells in blood prior to RA flares was of particular interest because others had shown that RA synovial fibroblasts can spread arthritis and function as critical gatekeepers of synovial inflammatory infiltrates in animal models," asserts Orange.

As only four patients were involved in the long-term monitoring in this study, further research will be needed to ascertain if PRIME cells precede disease flares in all patients with RA, and in patients with all types of RA. Orange and colleagues also hope to investigate possible mechanisms by which the B cells that emerge 2 weeks before a flare might activate or recruit the PRIME cells.

Joanna Clarke

ORIGINAL ARTICLE Orange, D. E. et al. RNA identification of PRIME cells predicting rheumatoid arthritis flares. *N. Engl. J. Med.* **383**, 218–228 (2020)