

IN BRIEF

CONNECTIVE TISSUE DISEASE

GWAS expands list of Sjögren syndrome risk loci

The largest genome-wide association study (GWAS) of Sjögren syndrome performed to date in individuals of European ancestry (3,232 cases, 17,481 controls) has identified 10 novel regions with genome-wide significance, bringing the total number of known genetic risk loci up from 12 to 22. Fine-mapping and bioinformatic analyses undertaken to determine the functional implications of the novel loci revealed regulatory networks that collectively influence the expression of >40 genes, including genes linked to immune cells and salivary gland dysfunction.

ORIGINAL ARTICLE Khatri, B. et al. Genome-wide association study identifies Sjögren's risk loci with functional implications in immune and glandular cells. *Nat. Commun.* **13**, 4287 (2022)

AUTOIMMUNITY

Omicron evades immunity from vaccines

After administration of a third dose of mRNA vaccine, mean cross-neutralizing antibody responses against the Omicron variant of SARS-CoV-2 were 50.3% in health-care workers but only 26.8% in patients with autoimmune rheumatic diseases (ARDs) in an observational cohort study. Responses capable of neutralizing the Omicron variant were detected in only 39.2% of sera from patients with ARDs who received a third dose of mRNA vaccine. Among the 19 patients with ARDs with confirmed breakthrough infections in the subsequent observation period, 14 (73.7%) had not reached the Omicron-neutralization capacity threshold pre-infection.

ORIGINAL ARTICLE Kim, W.-J. et al. SARS-CoV-2 Omicron escapes mRNA vaccine booster-induced antibody neutralisation in patients with autoimmune rheumatic diseases: an observational cohort study. *Ann. Rheum. Dis.* <https://doi.org/10.1136/ard-2022-222689> (2022)

COVID-19

NETs implicated in COVID-19 in kids and adults

Findings from a multi-cohort analysis indicate that levels of neutrophil extracellular trap (NET) remnants are elevated in paediatric patients affected by multi-system inflammatory syndrome in children or chilblain-like lesions (also known as 'COVID toes'), as well as in adults with symptomatic COVID-19, and were associated with clinical outcomes. Impaired NET degradation was observed in both adult and paediatric populations; these impairments did not seem to be genetically driven and were considered to be multifactorial.

ORIGINAL ARTICLE Carmona-Rivera, C. et al. Multicenter analysis of neutrophil extracellular trap dysregulation in adult and pediatric COVID-19. *JCI Insight* <https://doi.org/10.1172/jci.insight.160332> (2022)

PAEDIATRIC RHEUMATOLOGY

SARS-CoV-2 vaccine safe for young patients

Data from the EULAR COVAX physician-reported registry indicate that disease flares and serious adverse events rarely occur after SARS-CoV-2 vaccination in adolescents with inflammatory rheumatic and musculoskeletal diseases (RMD) and adults with juvenile idiopathic arthritis (JIA). RMD flare occurred in 1 of the 36 adolescents and 2 of the 74 adults in the dataset; only one serious adverse event was reported, in the adolescent group. Mild to moderate adverse events were common, but their frequency and profile was similar to that seen in the general population.

ORIGINAL ARTICLE Lawson-Tovey, S. et al. SARS-CoV-2 vaccine safety in adolescents with inflammatory rheumatic and musculoskeletal diseases and adults with juvenile idiopathic arthritis: data from the EULAR COVAX physician-reported registry. *RMD Open* **8**, e002322 (2022)

SYSTEMIC LUPUS ERYTHEMATOSUS

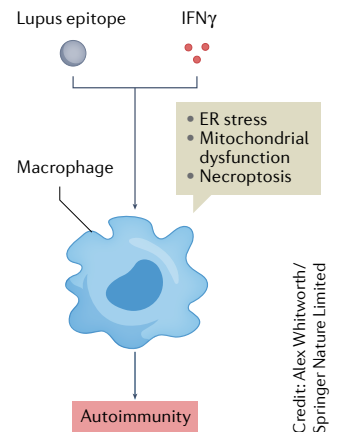
New evidence for the 'cusp theory' to explain HLA associations in SLE

HLA molecules convey the strongest genetic association in many autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). However, the molecular basis for these associations is often unclear. New findings support the existence of an antigen presentation-independent mechanism of autoimmunity and highlight the involvement of a newly discovered 'lupus epitope' in SLE susceptibility.

"Antigen presentation is the best-studied function of HLA molecules, and the mechanism that is widely postulated to underlie HLA-disease associations in rheumatic conditions," explains corresponding author Joseph Holoshitz. "This latest study is an extension of our research efforts over the past two decades validating a new mechanistic basis for HLA disease associations, designated the 'cusp theory'."

The cusp theory postulates that HLA molecules can facilitate autoimmunity independently of antigen presentation via a conserved cusp-like region that, under certain conditions, binds to non-MHC receptors to trigger aberrant cellular events and propagate disease. This cusp-like region encompasses the third allelic hypervariable regions (TAHRs) of the DR β chain and contains the 'shared epitope' in RA-associated HLA-DRB1 molecules, a 'protective epitope' in various HLA-DRB1 molecules associated with disease protection and a 'lupus epitope' in the SLE-associated molecule HLA-DRB1*03:01.

The researchers initially investigated the effects of various TAHR peptides (containing either the shared epitope, protective epitope or lupus epitope) and IFN γ on mouse (RAW 264.7) and human (THP-1) macrophage cell lines. Overall, RNA sequencing analysis revealed the upregulation of distinct, epitope-specific and disease-relevant patterns of expression. Notably, in the presence of IFN γ , the lupus epitope-containing TAHR peptide



(referred to as 65-79*LE) stimulated the expression of multiple SLE-associated genes, including those relating to type I interferon signalling.

In terms of cell functions, the researchers found evidence of endoplasmic reticulum stress, the unfolded protein response and mitochondrial dysfunction in IFN γ -stimulated macrophages treated with 65-79*LE. Further analysis suggested that the 65-79*LE peptide accelerated cell death via necroptosis and promoted the release of pro-inflammatory cytokines.

Exposure of primary bone marrow-derived macrophages from *DRB1*03:01* transgenic mice to IFN γ resulted in similar SLE-like patterns of gene expression and cellular abnormalities *ex vivo* and, *in vivo*, administration of IFN γ led to SLE-like features such as autoantibody production and glomerulonephritis.

Going forwards, Holoshitz and colleagues would like to identify the lupus epitope-binding receptor, with the long-term goal of developing small-molecule inhibitors to this receptor, similar to their ongoing efforts with the shared epitope. "Small-molecule inhibitors of shared-epitope interactions with cell surface receptors have been successfully developed, and one of them is being actively studied in human trials," reveals Holoshitz.

Jessica McHugh

ORIGINAL ARTICLE Miglioranza Scavuzzi, B. et al. The lupus susceptibility allele *DRB1*03:01* encodes a disease-driving epitope. *Commun. Biol.* **5**, 751 (2022)