Immunometabolism

mTORC1 implicated in Still's disease and MAS

The results of a new study show that the metabolic regulator mammalian target of rapamycin (mTORC1) has a role in the pathophysiology of Still's disease, encompassing systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD), and in the development of macrophage activation syndrome (MAS). "Using multiple mouse models, transcriptomic datasets, and patient samples, we found that mTORC1 is a missing link that connects the pathologic spectrum of Still's disease and MAS," reports author Peter Nigrovic, co-corresponding author with Pui Y. Lee.

The researchers studied mice deficient in the endogenous IL-1 receptor antagonist (*Il1rn*$^{-/-}$ mice) as a model of IL-1-driven inflammation in Still's disease. Single-cell RNA sequencing revealed enhanced activation of the mTORC1 pathway in monocytes from *Il1rn*$^{-/-}$ mice. Treatment of these mice with the mTORC1 inhibitor rapamycin attenuated features of systemic inflammation and also suppressed the development of joint inflammation and bone erosion. Depletion of monocytes using clodronate liposomes was also able to reduce arthritis severity and bone erosion.

In a mouse model of CpG-induced MAS, treatment with rapamycin reversed the enhanced mTORC1 activation seen in monocytes, and also lessened the severity of cytopenia, hyperferritinaemia and hepatosplenomegaly. In a separate mouse model, mice with induced deletion of the mTORC1 inhibitor *Tsc2*, which leads to unrestricted mTORC1activation, developed arthritis and an MAS-like syndrome, features of which could be prevented by treatment with rapamycin.

Analysis of human transcriptomic data from patients with sJIA or AOSD identified an mTORC1 gene signature that was correlated with disease activity and treatment response. Evidence of prominent mTORC1 activation was also found in haemophagocytic histiocytes from patients with MAS associated with Still's disease.

"These findings place Still's disease and MAS on a continuum of mTORC1 activation, and are clinically relevant because medications that inhibit the mTOR pathway are already in clinical use," Nigrovic notes. "More broadly, this study shows that derangement of immunometabolism can drive the development of systemic inflammatory disease, including Still's disease."

The findings provide a rationale for further exploration of the use of mTORC1 inhibitors for the treatment of sJIA, AOSD and MAS. Orally available mTORC1 inhibitors could present a less-expensive alternative to biologic agents, or an additional option for the treatment of refractory disease, although further testing of the efficacy and safety of this approach is required.

Sarah Onuora

Original article: Huang, Z. et al. mTORC1 links pathology in experimental models of Still's disease and macrophage activation syndrome. *Nat. Commun.* **13**, 6915 (2022)

In brief

Rheumatoid arthritis

Cancer and cardiovascular risk with JAK inhibition

In the ORAL Surveillance trial — a post-marketing trial comparing the safety and efficacy of the Janus kinase inhibitor tofacitinib with anti-TNF therapy in older patients with rheumatoid arthritis and cardiovascular risk factors — tofacitinib therapy was associated with a higher risk of malignancy. In a post-hoc analysis of this trial, the most frequently reported malignancy among the tofacitinib-treated patients was lung cancer. The incidence of malignancy was highest in those patients with a history of atherosclerotic cardiovascular disease or those who had a high cardiovascular risk score at baseline, suggesting that cardiovascular disease and cancer have shared risk factors in these patients.

Original article: Curtis, J. R. et al. Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: results from the open-label, randomised controlled ORAL Surveillance trial. *Ann. Rheum. Dis.* https://doi.org/10.1136/ard-2022-222543 (2022)

Systemic lupus erythematosus

Long-term anifrolumab safe in SLE

In a long-term extension study of the TULIP trials, assessing the safety and tolerability of the type I interferon receptor antagonist anifrolumab in patients with systemic lupus erythematosus, the benefit-to-risk profile of anifrolumab remained favourable after 3 years of treatment. The exposure-adjusted incidence rate (EAIR) of serious adverse events was comparable between the anifrolumab group and placebo group (8.5 versus 11.2), as were the EAIRs of non-opportunistic serious infections, malignancy and major acute cardiovascular events. The exposure-adjusted event rate of COVID-19-related adverse events was higher in the anifrolumab group than in the placebo group (15.5 versus 9.8), but no COVID-19-related adverse events occurred in fully vaccinated individuals.

Original article: Kalunian, K. C. et al. A randomized, placebo-controlled phase III extension of anifrolumab in active systemic lupus erythematosus. *Arthritis Rheumatol.* https://doi.org/10.1002/art.42392 (2022)

Psoriatic arthritis

Bimekizumab safe and effective for psoriatic arthritis

Dual inhibition of IL-17A and IL-17F with bimekizumab leads to superior improvements in joint and skin outcomes compared with placebo in patients with active psoriatic arthritis who are either naive to biologic DMARDs or who have had a previous inadequate response or intolerance to TNF inhibition, according to results from the BE OPTIMAL and BE COMPLETE phase III clinical trials. At 16 weeks, more patients reached an ACR50 response in the treatment groups than in the placebo groups (44% versus 10% for the BE OPTIMAL trial; 43% versus 7% for the BE COMPLETE trial). The safety profile of bimekizumab was consistent with previous reports.

Original articles: Merola, J. F. et al. Bimekizumab in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor-α inhibitors: a randomised, double-blind placebo-controlled, phase 3 trial (BE COMPLETE). *Lancet* https://doi.org/10.1016/S0140-6736(22)02303-0 (2022); McInnes, I. B. et al. Bimekizumab in patients with active psoriatic arthritis, naïve to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL). *Lancet* https://doi.org/10.1016/S0140-6736(22)02302-9 (2022)