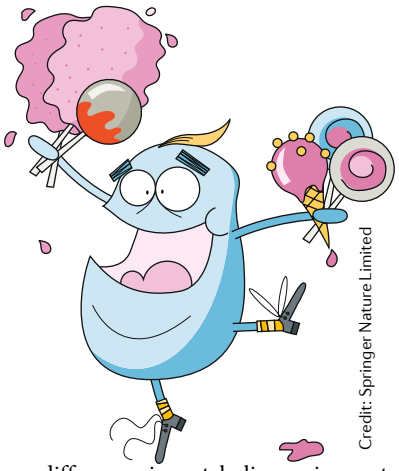
SYSTEMIC LUPUS ERYTHEMATOSUS

Targeting autoimmune-specific metabolic processes



Credit: Springer Nature Limited

Follicular helper T (T_{FH}) cells are involved in both the pathogenesis of systemic lupus erythematosus (SLE) and in protective humoral immune responses to pathogens, making these cells a challenge to target therapeutically. Addressing this challenge, the results of a new study show how blocking glucose metabolism can selectively eliminate autoreactive T_{FH} cells without compromising T cell-dependent responses to immunization or viral infection.

Previous investigations have revealed that inhibiting both glucose metabolism and mitochondrial metabolism reverses autoimmune pathology in lupus-prone mice. "In this study, we performed a detailed analysis of the metabolic requirements of T_{FH} cells from lupus-prone mice as compared with non-autoimmune controls," says corresponding author Laurence Morel. "Spontaneous autoreactive T_{FH} cells, but not influenza virus-specific T_{FH} cells demanded a high level of glucose metabolism."

Treatment with 2-deoxyglucose (2DG), an inhibitor of glycolysis and, hence, of glucose metabolism, prevented the expansion of T_{FH} cells in four mouse models of SLE. However, this treatment did not impair T cell-dependent humoral responses to exogenous antigen, nor did it impair influenza virus-mediated induction of antigen-specific T_{FH} cells. Conversely, inhibition of glutaminolysis with the glutamine analogue 6-diazo-5-oxo-L-norleucine reduced the production of both antigen-specific antibodies and autoantibodies. The results suggest that, unlike the unique requirement for high levels of glucose in autoreactive T_{FH} cells, all T_{FH} cells require glutamine. Overall, the findings highlight the qualitative differences in metabolic requirements between autoreactive T_{FH} cells and pathogen-specific T_{FH} cells.

> "blocking glucose metabolism can selectively eliminate autoreactive T_{FH} cells"

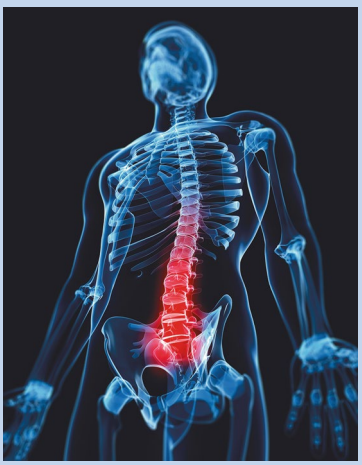
"We are now focusing on the mechanisms responsible for the higher glucose requirements of autoreactive T_{FH} cells, and what metabolites generated from glucose are specifically required," says Morel. "We plan also to use other pathogens to understand to what extent our results obtained with influenza virus infection and nominal protein immunization can be generalized."

Jessica McHugh

ORIGINAL ARTICLE Choi, S.-C. et al. Inhibition of glucose metabolism selectively targets autoreactive follicular helper T cells. *Nat. Commun.* **9**, 4369 (2018)

SPONDYLOARTHRITIS

Selective JAK inhibition for AS



Credit: Science Photo Library/Alamy Stock Photo

Selective inhibition of Janus kinase 1 (JAK1) is safe and effective for treating ankylosing spondylitis (AS) in patients who fail to respond to NSAIDs, according to the results of a new phase II, placebo-controlled trial published in *The Lancet*.

Unlike for psoriatic arthritis, inhibition of IL-6 or IL-23 was not effective for treating AS, meaning that current treatment options for patients with AS who do not respond well to NSAIDs are limited to TNF inhibitors and the anti-IL-17A antibody secukinumab. Tofacitinib (a dual JAK1 and JAK3 inhibitor) was effective in a phase II clinical trial, but safety issues are potentially a greater concern when blocking multiple JAKs.

In the current study, 116 patients from seven European countries were randomly allocated 1:1 to receive either 200 mg oral filgotinib (a JAK1 inhibitor) or placebo once daily for 12 weeks. All patients fulfilled the modified New York classification criteria for AS, had previously had an inadequate response to two or more NSAIDs and had radiographically confirmed sacroiliitis and active disease (Bath AS disease activity index (BASDAI) of ≥4 and C-reactive protein concentration of ≥3.0 mg/L).

> "current treatment options … are limited to TNF inhibitors and the anti-IL-17A antibody secukinumab"

"The primary endpoint was the change from baseline in the AS disease activity score (ASDAS)," explains corresponding author Désirée van der Heijde. "This was the first time that this endpoint was used as a primary endpoint for a phase II or III trial." At week 12, the change in ASDAS from baseline was −1.47 (SD 1.04) for those treated with filgotinib and −0.57 (SD 0.82) for those who received placebo (least squares mean difference between groups of −0.85; 95% CI −1.17 to −0.53; $P<0.0001$). The number of reported adverse events was equal in each group and one patient in each group withdrew owing to an adverse event (pneumonia in the filgotinib group and high creatine kinase in the placebo group).

"The data show that selective inhibition of JAK1 may be an effective and safe treatment option for patients with active AS who failed treatment with NSAIDs," says van der Heijde. "Phase III trials should confirm these findings."

Joanna Collison

ORIGINAL ARTICLE van der Heijde, D. et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* https://doi.org/10.1016/S0140-6736(18)32463-2 (2018)