RHEUMATOID ARTHRITIS

Sulf2 mediates the effects of TNF in RASFs

Extracellular sulfatase Sulf2, an enzyme that modulates the binding site of various growth factors and cytokines, has been identified as a therapeutic target in cancer but has remained largely uninvestigated in the context of inflammation and rheumatoid arthritis (RA). New evidence now implicates Sulf2 in TNF-mediated pro-inflammatory signalling in RA synovial fibroblasts (RASFs) and suggests that targeting this enzyme could have therapeutic potential.

The researchers first determined that the expression of Sulf2 is increased in synovial tissue and sera from patients with RA compared with tissue and sera samples from healthy individuals; Sulf2 expression was also elevated in the inflamed joints of human TNF transgenic (hTNFtg) mice. In vitro, stimulation of human RASFs with TNF transiently induced the expression of Sulf2.

RNA-sequencing analysis revealed that the induction of many pro-inflammatory genes in RASFs in response to TNF is dependent on Sulf2: knockdown of Sulf2 in RASFs with small interfering RNA (siRNA) altered the expression of ~2,500 genes, including a number of genes implicated in RA pathogenesis. Consistent with these findings, siRNA-mediated Sulf2 knockdown or pre-treatment of RASFs with the Sulf2 inhibitor OKN-007 inhibited the TNF-induced expression of adhesion proteins and chemokines.

Silencing of Sulf2 abrogated TNF-induced activation of the PKCδ and JNK signalling pathways and the nuclear translocation and activity of the pro-inflammatory transcription factors AP-1 and NF-κB. In addition, Sulf2 knockdown inhibited TNF-induced proliferation of RASFs, suggesting that inhibiting Sulf2 could limit synovial hyperplasia.

The researchers propose that further studies are warranted to test the therapeutic potential of Sulf2 inhibition for the treatment of RA.

Sarah Onuora

ORIGINAL ARTICLE Siegel, R. J. et al. Extracellular sulfatase-2 is overexpressed in rheumatoid arthritis and mediates the TNF-α-induced inflammatory activation of synovial fibroblasts. *Cell. Mol. Immunol.* https://doi.org/10.1038/s41423-022-00913-x (2022)

COVID-19

Optimizing methotrexate withdrawal during COVID vaccination

Methotrexate, an immunosuppressant commonly used for the treatment of autoimmune inflammatory arthritis, reduces the immunogenicity of COVID-19 vaccination, necessitating an optimized strategy for maximizing the vaccine response while controlling disease activity in these patients. Results from a new study published in *Lancet Rheumatology* suggest that withdrawal of methotrexate only after the second dose of a COVID vaccine is safe and effective in patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA).

The study presents the results of two parallel, assessor-masked randomized controlled trials: MIVAC I and MIVAC II. These trials assessed the effects of withholding methotrexate for 2 weeks after the first and second doses (MIVAC I) or after the second dose only (MIVAC II) of the ChAdOx1 nCoV-19 vaccine in patients with RA or PsA versus continuing treatment with methotrexate throughout.

In both trials, withholding methotrexate resulted in a higher anti-receptor binding domain (RBD) antibody titre 4 weeks after the second dose (the primary outcome) than continuation of methotrexate. In MIVAC II, but not in MIVAC I, the proportion of patients with a flare did not differ between the methotrexate hold group and the methotrexate continuation group.

Post-hoc analysis found no difference in anti-RBD antibody titres between participants who withheld methotrexate twice and those who withheld methotrexate only after the second vaccine dose. Overall, the results suggest that withholding methotrexate only after the second dose is as effective in improving the vaccine response as withholding methotrexate after both vaccine doses, and does not increase the risk of flare.

Jessica McHugh

ORIGINAL ARTICLE Skaria, T. G. et al. Withholding methotrexate after vaccination with ChAdOx1 nCov19 in patients with rheumatoid or psoriatic arthritis in India (MIVAC I and II): results of two, parallel, assessor-masked, randomised controlled trials. *Lancet Rheumatol.* https://doi.org/10.1016/S2665-9913(22)00228-4 (2022)

SYSTEMIC SCLEROSIS

Thy-1 promotes skin fibrosis in SSc

New research suggests that the Thy-1 membrane glycoprotein (CD90) is a biomarker with a pathogenic role in skin fibrosis in systemic sclerosis (SSc).

Thy-1 is expressed in several cell types, including fibroblasts, and its functions are thought to depend on the cell type and physiological context. In a new study, immunofluorescence staining of human biopsy-derived skin samples identified a higher proportion of cells in the reticular dermis that were positive for Thy-1 in patients with SSc than in healthy individuals. In SSc, Thy-1 positivity was also higher in patients with a disease duration of >3 years than in those with early disease.

THY1 expression in human skin was analysed in two microarray datasets, and found to be higher in patients with either limited SSc or diffuse cutaneous SSc than in healthy individuals, correlating with the severity of skin involvement.

In mice expressing a Thy-1–yellow fluorescent protein (YFP) fusion protein, induction of fibrosis by injection with bleomycin resulted in progressive elevation of Thy-1–YFP expression that correlated with the extent of fibrosis. Whole-animal fluorescence imaging with this mouse model could enable non-invasive assessment of fibrosis in longitudinal pharmacological studies.

Knockout of *Thy1* expression in mice attenuated bleomycin-induced skin fibrosis, reducing numbers of infiltrating macrophages, expression of several genes associated with inflammatory pathways, and numbers of myofibroblasts in the skin.

The involvement of Thy-1 in multiple fibrotic pathways was further investigated by RNA sequencing of skin tissue, to identify genes that were differentially expressed in mice treated with phosphate-buffered saline compared with those treated with bleomycin. Notably, many fewer such genes were identified in *Thy1*-knockout mice than in wild-type mice, consistent with the attenuation of fibrosis in this model. The expression of genes involved in several fibrotic pathways was upregulated in bleomycin-treated wild-type mice, but not in bleomycin-treated *Thy1*-knockout mice.

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ORIGINAL ARTICLE Marangoni, R. G. et al. Thy-1 plays a pathogenic role and is a potential biomarker for skin fibrosis in scleroderma. *JCI Insight* https://doi.org/10.1172/jci.insight.149426 (2022)