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OSTEOARTHRITIS

TET1: an epigenetic controller of OA

Osteoarthritis (OA) is a heterogeneous disease mediated by multiple molecular pathways and governed by a complex interplay between various genetic, epigenetic and environmental factors. New findings published in *Science Translational Medicine* implicate the epigenetic regulator ten-eleven translocation 1 (TET1) as an important activator of multiple OA-associated pathways and as an attractive therapeutic target.

TET enzymes catalyse the initial step of DNA demethylation by converting 5-methylcytosine into 5-hydroxymethylcytosine (5hmC), an epigenetic process associated with gene activation. Previous evidence had shown that 5hmC accumulates on OA-related genes in osteoarthritic chondrocytes. To investigate this process further, the authors of the new study mapped changes in the 5hmC epigenome in mice following induction of OA by destabilization of the medial meniscus (DMM), with and without the expression of *Tet1*.

In wild-type mice, OA induction was accompanied by a genome-wide accumulation of 5hmC, predominantly in gene bodies or intergenic regions, and an upregulation in expression of hundreds of genes. Notably, almost half of the upregulated genes gained sites of 5hmC accumulation, including genes involved in WNT signalling, protein kinase A signalling and inositol metabolism.

The majority of 5hmC deposition was lost in mice lacking TET1. Importantly, loss of *Tet1* impeded the initiation and development of DMM-induced OA, including the deterioration of cartilage and osteophyte formation.

> “OA induction was accompanied by a genome-wide accumulation of 5hmC”

TET1 activated various pathways important in OA pathogenesis, including WNT signalling, metalloproteinases and STAT3 signalling. Indeed, shRNA-mediated knockdown of TET1 in chondrocytes from patients with OA decreased the expression of *MMP3* and *MMP13*.

To provide proof of principle that modulating TET1 activity is a promising therapeutic strategy, the researchers tested a small molecular inhibitor of TET1, 2-hydroxyglutarate (2-HG). Intra-articular injection of 2-HG after DMM surgery stalled OA progression in mice, and this inhibitor could replicate the effects of TET1 knockdown in osteoarthritic chondrocytes in vitro.

Jessica McHugh

ORIGINAL ARTICLE Smeriglio, P. et al. Inhibition of TET1 prevents the development of osteoarthritis and reveals the 5hmC landscape that orchestrates pathogenesis. *Sci. Transl Med.* **12**, eaax2332 (2020)
RELATED ARTICLE Rice, S. J. et al. Interplay between genetics and epigenetics in osteoarthritis. *Nat. Rev. Rheum.* **16**, 268–281 (2020)

RHEUMATOID ARTHRITIS

Targeting FLS signalling in RA

Fibroblast-like synoviocytes (FLS) can promote joint inflammation and destruction in rheumatoid arthritis (RA) through the production of pro-inflammatory mediators such as IL-15 and dickkopf-related protein 1 (DKK1). New findings published in *Arthritis & Rheumatology* highlight the involvement of a signalling axis downstream of discoidin domain receptor 2 (DDR2) in this process.

Previous studies had suggested that DDR2, a receptor tyrosine kinase (RTK), is expressed in FLS and contributes to cartilage and bone destruction in RA. In the new study, the researchers found that the expression of DDR2 correlated with the expression of IL-15 and DKK1 both in FLS from patients with RA (RA FLS) and in mice with collagen antibody-induced arthritis (CAIA).

Following collagen antibody treatment, *Ddr2*$^{-/-}$ mice had milder arthritis than wild-type mice and reduced expression of both IL-15 and DKK1. Restoring the expression of DDR2 in the joints of *Ddr2*$^{-/-}$ mice using a DDR2-expressing adenovirus increased the arthritis severity score as well as the expression of IL-15 and DKK1.

> “treatment with WRG-28 was associated with reduced clinical arthritis scores”

In vitro experiments in RA FLS identified the long non-coding RNA H19 as a downstream target of the DDR2 signalling cascade. H19 could then interact with and downregulate miR-103a, a microRNA previously shown to be downregulated in RA FLS. Notably, the predicted targets of this microRNA included *IL15* and *DKK1*, and, indeed, data from dual luciferase reporter assays suggested that miR-103a could directly target and repress the expression *IL15* and *DKK1*.

“DDR2 can be blocked by several FDA-approved RTK inhibitors, such as dasatinib and imatinib, and a recent study has shown that inhibition of DDR2 by dasatinib attenuates inflammation severity and bone destruction in mice with CAIA and RA FLS,” explains corresponding author Wei Zhang. Given the low specificity of dasatinib for DDR2, Zhang and colleagues explored the potential of a more recently developed small molecule inhibitor of DDR2, WRG-28.

In the CAIA model, treatment with WRG-28 was associated with reduced clinical arthritis scores, as well as reduced levels of inflammatory cell infiltration and destruction of cartilage and bone. In line with the proposed DDR2–H19–miR-103a signalling axis, WRG-28 treatment was also associated with decreased expression of H19, IL-15 and DKK1 and increased expression of miR-103 in the ankle joints of the mice.

Jessica McHugh

ORIGINAL ARTICLE Mu, N. et al. Blockade of discoidin domain receptor 2 as a strategy for reducing inflammation and joint destruction in rheumatoid arthritis via altered interleukin-15 and Dkk-1 signaling in fibroblast-like synoviocytes. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41205 (2020)
RELATED ARTICLES Nygaard, G. & Firestein, G. S. et al. Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes. *Nat. Rev. Rheum.* **16**, 316–333 (2020)