PAEDIATRIC RHEUMATOLOGY

Some PD-1$^+$ CD8$^+$ T cells are not exhausted

New research shows that PD-1$^+$ CD8$^+$ T cells that accumulate in the synovial fluid of patients with juvenile idiopathic arthritis (JIA) are not in an exhausted state. These cells are mostly memory T cells with an effector signature and probably derive from local antigenic stimulation to contribute to joint pathology.

PD-1 is a negative co-stimulatory receptor best known for its function as an immune checkpoint. In chronic inflammatory environments such as cancer and some infectious diseases, PD-1 expression is induced on CD8$^+$ T cells and is associated with loss of effector functions and the entry of those cells into a state known as exhaustion.

To see if PD-1$^+$ CD8$^+$ T cells in the joints are similarly exhausted, the researchers performed whole-transcriptome sequencing of T cell subsets from the synovial fluid of patients with JIA or from healthy individuals. The JIA PD-1$^+$ cells were enriched for gene expression pathways that are typical of effector T cells, such as the cell cycle, proliferation, cytotoxicity and pro-inflammatory signalling.

The researchers also showed that these PD-1$^+$ cells are primarily glycolytic and have not switched cellular metabolism to oxidative phosphorylation, as is expected of exhausted T cells. Furthermore, these cells were functionally active in response to in vitro stimulation with PMA and ionomycin or with anti-CD3 and anti-CD28 antibodies.

The researchers also characterized the T cell receptor (TCR) Vβ repertoires, showing that TCR diversity is lower in the PD-1$^+$ subset than in the PD-1$^-$ population, suggesting that PD-1$^+$ cells in the synovial fluid of patients with JIA proliferate in response to locally expressed antigens and that PD-1 marks a distinct CD8$^+$ T cell subset.

"At the target site of chronic inflammatory diseases, enrichment

> "…PD-1$^+$ cells are primarily glycolytic and have not switched cellular metabolism to oxidative phospho-rylation…

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of PD-1$^+$ CD8$^+$ T cells doesn't mean exhaustion, but rather functional adaptation and local antigen-driven clonal expansion," explains Alessandra Petrelli, first author of the new study. "Therefore, our paper supports the idea of functional T cell adaptation to the local inflammatory environment. The data also suggest that these cells may have a pathogenic function in chronic inflammation and could be interesting targets for therapy," she concludes.

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ORIGINAL ARTICLE Petrelli, A. et al. PD-1$^+$CD8$^+$ T cells are clonally expanding effectors in human chronic inflammation. *J. Clin. Invest.* https://doi.org/10.1172/JCI96107 (2018)

OSTEOARTHRITIS

Brains and bones and joints

The nuclear phosphoprotein ANP32A protects against oxidative degeneration of brain, bone and cartilage tissue, according to a study published in *Science Translational Medicine*.

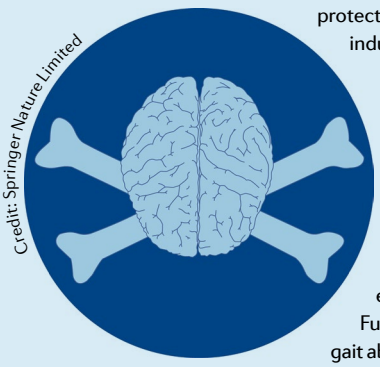
To understand an already established association between risk of osteoarthritis and *ANP32A* polymorphisms, the researchers show that compared with patients admitted for trauma surgery, patients with hip osteoarthritis (OA) have lower gene and protein expression of ANP32A in cartilage. The protein is also expressed less in damaged areas than in healthy areas of the cartilage.

These findings are mirrored in both surgically-induced and age-induced mouse models of OA. Furthermore, *Anp32a*$^{-/-}$ mice are more susceptible to cartilage degeneration in a variety of OA models.

To understand the mechanism of this protective function of ANP32A, the researchers conducted genome-wide transcriptomic analyses. One of the top hits, *Atm*, drew their attention owing to the known anti-oxidant function of the protein kinase it encodes. They show that *Atm* is barely expressed in cartilage from *Anp32a*$^{-/-}$ mice and in patients with OA, especially in damaged areas of cartilage, and knockdown of *ANP32A* in human cartilage samples results in lower expression of *ATM*.

Using ChIP-qPCR and RNA polymerase II analysis the researchers found that ANP32A directly activates transcription at the *ATM* promoter in chondrocytes.

The therapeutic implications of these findings were probed by feeding the antioxidant *N*-acetyl-cysteine (NAC) to *Anp32a*$^{-/-}$ mice, resulting in cartilage protection against surgically induced OA.



Credit: Springer Nature Limited

Intriguingly, the pathology in *Anp32a*$^{-/-}$ mice is not restricted to cartilage as the mice also developed osteopenia plus ataxia that is associated with reduced cerebellar expression of *Atm*. Furthermore, the ataxic gait abnormality in these mice was reversed by NAC treatment.

"Oxidative stress has been suggested to play an important role in the progression of osteoarthritis and other degenerative or ageing-associated diseases," explains corresponding author Rik Lories. "Our data suggest that increasing levels of ANP32A in the target tissues may be a strategy to act against these processes and treat OA and other diseases," he concludes.

> "…*Anp32a*$^{-/-}$ mice are more susceptible to cartilage degeneration…

Nicholas J. Bernard

ORIGINAL ARTICLE Cornelis, F. M. F. et al. ANP32A regulates ATM expression and prevents oxidative stress in cartilage, brain, and bone. *Sci. Transl. Med.* **10**, eaar8426 (2018)