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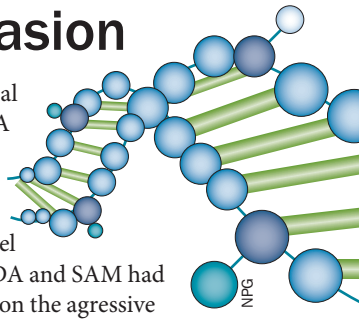
RHEUMATOID ARTHRITIS

SSAT1 inhibition slows synovial fibroblast invasion



The pathogenic behaviour of synovial fibroblasts (SFs) in rheumatoid arthritis (RA) seems to arise, at least in part, from epigenetic modifications including altered DNA methylation. Could pharmacologic therapy aimed at restoring DNA methylation in RASFs be a viable treatment approach to RA? New research suggests the key to success might be inhibition of an enzyme involved in the recycling of polyamines.

Spermidine/spermine N(1)-acetyltransferase [SSAT1]) causes excessive consumption of S-adenosylmethionine (SAM), a derivative of methionine that serves as a methyl donor in RASFs. Following their earlier research that validated SSAT1 as a therapeutic target in RA, Michel Neidhart and colleagues demonstrated that expression of SSAT1 was increased in SFs isolated from patients with RA compared with those from patients with osteoarthritis. Counter to their original hypothesis, this overexpression did not result from changes in PMF1 promoter methylation but rather was intrinsic to RASFs. The investigators also showed that increased levels of SSAT1 were responsible for decreased levels of SAM in RASFs.

Inhibition of SSAT1 activity with small interfering RNA or with the antiparasitic agent diminazene aceturate (DA) increased methylation in RASFs. DA also reduced adhesion and activation of RASFs. Notably, DA was more efficient in RASFs with high baseline levels of SSAT1, which occurred in cells from ~50% of patients.

Direct supplementation with SAM also increased methylation; could methyl donor replacement be a therapeutic option? "In RASFs with high levels of SSAT1," explains Neidhart, "the intrinsically activated metabolism of polyamines continues to consume SAM and thus does not enable restoration of DNA methylation." In such cases, he suggests, additional treatment with DA seems necessary.

Evaluating this approach in the SCID mouse model of arthritis, both DA and SAM had a beneficial effect on the agressive behaviour of RASFs, but the greatest benefit was seen with the combination of the two, which reduced the invasiveness of RASFs with high levels of SSAT1 by 70%.

Neidhart suggests that efforts should be directed at the development of highly specific inhibitors of SSAT1, which would then need to be tested in combination with SAM or methionine.

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Original article Neidhart, M. *et al.* Inhibition of spermidine/spermine N1-acetyltransferase (SSAT1) activity—a new therapeutical concept in rheumatoid arthritis. *Arthritis Rheum.* doi:10.1002/art.38574