RHEUMATOID ARTHRITIS

Choline kinase—more than a cancer therapy target?

“Blocking choline kinase suppressed the aggressive behavior of fibroblast-like synoviocytes in rheumatoid arthritis and was highly effective in a preclinical model of arthritis,” says Monica Guma, corresponding author of a study published in *Annals of the Rheumatic Diseases*.

Choline kinase is a phosphotransferase enzyme that catalyzes the conversion of choline to phosphocholine, a first step in the biosynthesis of phosphatidylcholine (see figure). Phosphatidylcholine metabolism affects cell proliferation, migration and signalling, and through these mechanisms is thought to be an important regulator of tumorigenesis.

In explanation of why her group began studying metabolic abnormalities in RA, Guma says, “Targeting the metabolome in cancer is now emerging as a potential therapeutic approach. The joint in RA has many characteristics of tumors, including hypoxia and high levels of oxygen radicals, nitric oxide and cytokines.”

By immunohistochemistry, western blot and ^1H magnetic resonance spectroscopy, the researchers showed choline kinase α is highly expressed in the synovium of patients with RA, particularly in the intimal layer, and also in *ex vivo* cultured fibroblast-like synoviocytes. Expression of the enzyme was shown to be induced by inflammatory stimuli, including TNF, IL-1 and platelet-derived growth factor, but not lipopolysaccharide.

The researchers found that mitogen-activated protein kinase and PI3K/Akt signalling by fibroblast-like synoviocytes could be reduced with a choline kinase inhibitor (MN58b). These data complement knowledge of the tumour cell biology and contribute to understanding of the mouse modelling data, that is, administration of MN58b reduced clinical scores of established disease severity in the K/BxN serum transfer mouse model of inflammatory arthritis, when compared with vehicle-treated control mice.

In reference to ongoing and planned work, the lead researcher of the study, Gary Firestein, comments, “We would like to determine the suitability of choline metabolites or other metabolites as biomarkers of fibroblast-like synoviocyte activation and joint damage in patients with RA. If successful, our studies could translate into important diagnostic and prognostic tests.”

Nicholas J. Bernard

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