RHEUMATOID ARTHRITIS

Another cog in the mechanism of methotrexate

Researchers in the UK have identified an AMP-activated kinase (AMPK) and cyclic AMP response element-binding protein (CREB) signalling pathway in the mechanism of methotrexate's capacity to reduce the risk and signs of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA).

Reducing endothelial cell dysfunction and the incidence of CVD are expected outcomes of methotrexate therapy, but, despite being the most commonly prescribed drug for RA, the mechanism of disease modification is not yet understood completely.

Metabolites of methotrexate were already known to induce AICAR monophosphate and AMP accumulation, which were thought to inhibit inflammation via adenosine release. This new study places AMPK as a central regulator of methotrexate's function.

To understand the signalling pathway, the researchers stimulated primary human endothelial cells with therapeutic doses (0.1–100 nM) of methotrexate. In addition to AMPK phosphorylation, Mn O₂ dismutase, the catalytic converter of superoxide to H₂O₂, was produced, and cytoprotective AMPK-dependent genes were expressed, including anti-inflammatory *HMOX1*.

Furthermore, 12-week-old male WBF₁ ([NZW×BXS_B]F₁) mice, which spontaneously develop SLE-like disease, were injected weekly with methotrexate (1 mg/kg) for 4 weeks, reducing the severity of vasculopathy and the incidence of myocardial infarction.

Bruce Cronstein, an independent expert from NYU Langone Medical Centre, says the conclusions are “nicely supported by the data,” but notes that protection could involve “other methotrexate effects, for example, adenosine receptor activation with downstream activation of a common transcriptional regulator, such as CREB”.

Cronstein cautions, “There is little evidence that other agents that activate AMPK, such as metformin, provide similar protection. Nonetheless, this work will have greater importance if ongoing trials of low-dose methotrexate for protection against development of atherosclerotic cardiovascular disease demonstrate a clinically significant effect.”

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Original article Thornton, C. C. *et al.* Methotrexate-mediated activation of an AMPK-CREB-dependent pathway: a novel mechanism for vascular protection in chronic systemic inflammation. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2014-206305