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ATHEROPROTECTIVE EFFECTS OF ADALIMUMAB AND RESVERATROL IN THP-1 HUMAN MACROPHAGES: CHANGES IN EXPRESSION OF PROTEINS INVOLVED IN LIPID EFFLUX

Oral Contributions
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Background: Premature atherosclerotic cardiovascular disease (ASCVD) is a common yet under-recognized problem in rheumatoid arthritis (RA). RA treatment with multiple disease modifying anti-rheumatic drugs can reduce atherosclerosis, but it is unclear which medications are most efficacious. This project investigated the effect of adalimumab (Humira), an anti-TNF agent, resveratrol, a dietary supplement, and methotrexate (MTX) on reverse cholesterol transport (RCT) in macrophages.

Methods: THP-1 human macrophages (106/ml), were incubated for 18h in media (control), adalimumab (50μg/ml), MTX (5μM) or resveratrol (10μM). Cholesterol influx was analyzed under identical conditions ± 5μg/ml dil-oxLDL. Message levels of the RCT proteins 27-hydroxylase, ABCA1 and ABCG1 were evaluated by real-time PCR. Protein levels were confirmed by Western blot. Cellular dil-oxLDL content was quantified by fluorescent intensity using confocal microscopy

Results: Adalimumab augmented expression of RCT proteins in THP-1 macrophages relative to untreated control (set at 100%) as follows: ABCA1- to 124±9.2% for mRNA and 184±12.2% for protein and ABCG1- to 122.4±9.2% for message and 171±19.1% for protein. MTX affected expression of ABCG1 but not ABCA1, increasing message to 153±5.6% and protein to 172±17.3% (n=3, $P<0.05$). MTX significantly increased 27-hydroxylase (by 153±4.6% for mRNA and 233±21.2% for protein) (n=3, $P<0.05$). Similarly, reseveratrol increased ABCA1 and ABCG1 message 174.5±4.6% and 187.3±5.3% (n=3, $P<0.001$), respectively. Protein expression was upregulated to 200±15.67% and 225.3±19.54% (n=3, $P<0.01$). Altered cholesterol efflux was accompanied by diminished oxLDL uptake: to 87.5% for adalimumab, 76.5% for MTX and 72.8% for resveratrol.

Conclusions: MTX, resveratrol and adalimumab enhance cholesterol efflux suggesting anti-atherosclerotic effects: MTX through ABCG1 and 27-hydroxylase, adalimumab and resveratrol through ABCG1 and ABCA1. Elucidation of specific effects on cholesterol handling may lead to an understanding of their influence on atheroma development. This could result in additional, more personalized approaches to ASCVD prevention and management.