Purpose The inflammation hypothesis of ageing suggests that molecular inflammation could be an underpinning of ageing and age-related diseases such as rheumatoid arthritis (RA). Besides, mitochondrial alterations may contribute to the progression of RA. In this study we investigated the relationship between mitochondrial dysfunction and the in vitro expression of cyclooxigenase-2 (COX-2), prostaglandin E2 (PGE2) and interleukin-8 (IL8) in normal human synoviocytes.

Method Commonly used inhibitors to induce mitochondrial dysfunction were employed (antimycin A (AA) and oligomycin (OLI), inhibitors of complexes III and V of mitochondrial respiratory chain (MRC), respectively) in synoviocytes. IL1β and tumour necrosis factor α (TNFα) were used as inflammatory mediators. To identify possible pathways we used N-acetylcysteine as ROS scavenger; the natural antioxidant resveratrol; and BAY as an inhibitor of NF-κ activation. COX-2 protein and mRNA expression and both PGE2 and IL8 levels were analysed by flow cytometry, RT-PCR and ELISA, respectively.

Results We found that exposure of synoviocytes to AA and OLI significantly increased COX-2 protein expression in a time- and dose-dependent manner. The maximal response was observed at 6 h with 20 µg/ml AA and 25 µg/ml OLI (3.0±0.3, $p<0.001$ and 6.5±1.9, $p<0.001$, respectively vs basal 1) while the positive control, 1 ng/ml IL1, expression was 12.6±3.4. Quantification of COX-2 mRNA expression at 4 h showed similar results. PGE2 levels were also increased when cells were stimulated for 9 h with OLI. We then determined if mitochondrial dysfunction could modulate the response induced by suboptimal doses of IL1 (0.1 ng/ml) on COX-2 protein expression and PGE2 production. We found that pretreatment of synoviocytes with 10 µg/ml OLI for 30 min significantly increased the IL1-induced COX-2 protein expression (32.5±2.5 OLI+IL1 vs 6.5±2.4 IL1 and 4.5±1.7 OLI, $p<0.001$) and COX-2 mRNA expression. Similar results were obtained when PGE2 production was assessed (277.0±67.6 OLI+IL1 vs 15.4±2.6 IL1 and 97.5±45.6 OLI, expressed as pg/50000 cells, n=duplicate, $p<0.005$). Equivalent results were observed when TNFα or AA was employed. We also explored whether OLI together with IL1 significantly potentiates the expression of the proinflammatory chemokine IL8. Finally, we observed that this inflammatory response was counteracted by the addition of N-acetylcysteine, resveratrol or BAY, demonstrating the involvement of ROS and NF-κB in this process.

Conclusion Besides inducing a slight inflammatory response, dysfunction of mitochondrial respiratory activity significantly potentiates the cytokine-induced inflammatory response in synoviocytes in relation to PGE2 and IL8 release via ROS production and NF-κB activation, contributing to chronic inflammation of synovial tissue in RA and ageing joints.

A143 A NOVEL ROLE FOR MITOCHONDRIAL DYSFUNCTION IN THE INFLAMMATORY RESPONSE OF RHEUMATOID ARTHRITIS

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