

Background Mutated mitochondrial DNA (mtDNA) may be resultant to inflammation or pathogenic of itself in rheumatoid arthritis (RA)/psoriatic arthritis (PsA). Mitochondria are a rich source of reactive oxygen species (ROS) which are harmful to mtDNA. Tumour necrosis factor α (TNF α) increases mitochondrial ROS production and may thus induce mtDNA mutagenesis which the authors sought to investigate both in vivo and ex vivo.

Methods 39 RA and 11 PsA patients with active disease contributed synovial tissue at arthroscopy with a subgroup (n=12) contributing tissue pre/post anti-TNF α therapy. Normal synovial biopsies were obtained from 10 people undergoing interventional arthroscopy. Clinical, biochemical, microscopic and macroscopic measures of disease activity were discovered. To mimic the in vivo environment, human synoviocytes (K4's) were stimulated with TNF α (10 ng/ml) in the presence of adalimumab (ADA-5 μ g/ml) or isotype matched IgG control (5 μ g/ml). A mitochondrial random capture assay was used to quantify alterations in the mitochondrial genome in synovial biopsies. Intracellular ROS, mitochondrial membrane potential (MMP) and mitochondrial mass (MM) were quantified using fluorescent molecular probes. OCT embedded whole tissue samples were analysed by immunohistochemistry for T lymphocyte and macrophage infiltration. TNF α , interleukin 6 (IL-6), interferon γ (IFN γ), IL-1 β and IL-8 were measured in synovial fluid by MSD multiplex assays or specific ELISA.

Results A significant increase in the frequency of mtDNA mutation was demonstrated in synovial tissue from patients with RA/PsA compared to control tissue ($p < 0.05$). mtDNA mutation positively correlated with macroscopic synovitis ($p < 0.01$, $r = 0.52$) and vascularity ($p < 0.01$, $r = 0.54$) and with microscopic infiltration of T lymphocytes and macrophages to the synovial sublining layer ($p < 0.05$, $r = 0.46$, $r = 0.5$). mtDNA mutation positively correlated with synovial fluid levels of TNF α ($p < 0.01$, $r = 0.74$), IL-1 β and IFN γ ($p < 0.05$, $r = 0.65$, $r = 0.72$). The frequency of mtDNA mutation in synovial tissue reduced after anti-TNF α therapy in line with a good Disease Activity Score using 28 joint counts response ($p < 0.05$). Furthermore, in vitro stimulation with TNF α induced ROS production and mtDNA mutation by K4's compared to IgG controls. This effect was negated when K4's were costimulated with TNF α and ADA ($p < 0.05$). There was a concomitant rise in MM and MMP in TNF α treated K4's ($p < 0.05$) which again was negated by costimulation.

Conclusion Mutation of mtDNA is a pathologic feature of RA/PsA and is associated with macroscopic, microscopic and soluble markers of active disease. Anti-TNF α treatment reverses this phenomenon in vivo and in vitro which coincides with similar alterations in oxidative damage (ROS, MMP and MM). Together these results suggest mtDNA mutation and oxidative damage driven by TNF α are implicated in the pathogenesis of inflammatory arthritis.

A48 **THE MUTATION OF MITOCHONDRIAL DNA IS CENTRAL TO THE PATHOGENESIS OF RHEUMATOID AND PSORIATIC ARTHRITIS**

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