MITOCHONDRIAL DNA DAMAGE PROMOTES ATHEROSCLEROSIS AND CORRELATES WITH HIGHER RISK PLAQUE IN HUMANS

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Introduction Mitochondrial DNA (mtDNA) damage occurs in both the vessel wall and in circulating cells in human atherosclerosis. However, whether mtDNA damage directly promotes atherogenesis or is a consequence of tissue damage, and whether its effects are only mediated through reactive oxygen species (ROS) is unknown.

Methods We studied apolipoprotein E deficient mice, which were also deficient for mtDNA polymerase proof reading activity (PolG^{-/-}/ApoE^{-/-}). PolG^{-/-}/ApoE^{-/-} mice were assessed for the presence of atherosclerotic plaques, mtDNA damage, mitochondrial dysfunction and levels of ROS. We characterised phenotypic changes in vascular smooth muscle cells (VSMCs) and monocytes. To examine mtDNA damage in human atherosclerosis, we quantified the levels of damage in plaques, and in leukocytes from patients who had undergone intravascular ultrasound characterisation of coronary plaques.

Results PolG^{-/-}/ApoE^{-/-} mice showed extensive mtDNA damage, defects in oxidative phosphorylation but no increase in ROS. We found increased atherosclerosis in polG^{-/-}/ApoE^{-/-} mice, associated with impaired proliferation and apoptosis of VSMCs and hyperlipidaemia. In contrast, transplantation with polG^{-/-}/ApoE^{-/-} bone marrow increased features of plaque vulnerability, with increased apoptosis and inflammatory cytokine release of polG^{-/-}/ApoE^{-/-} monocytes. Consistent with these findings, human atherosclerotic plaques show increased mtDNA damage compared with normal vessels. Leukocyte mtDNA damage was associated with higher risk plaques but not plaque burden.

Conclusions MtDNA defects promote atherosclerosis and plaque vulnerability, independently of ROS, through effects on VSMCs, monocytes and hyperlipidaemia. Protection against mtDNA damage, and improvement of mitochondrial function, are potential areas for new therapeutics.