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Meeting abstract

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Functional consequences of mitochondrial DNA deletions in human skin fibroblasts: increased contractile strength in collagen lattices is due to oxidative stress-induced lysyl oxidase activity

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Deletions of the mitochondrial DNA (mtDNA) are thought to contribute to extrinsic skin aging, because they are found at increased amounts in photoaged skin and are induced through chronic UV irradiation in human skin fibroblasts *in vitro* and *in vivo*. In order to study how the presence of mtDNA deletions translates into functional and structural changes in the skin we have seeded human skin fibroblasts into collagen gels in order to generate human dermal skin equivalents. These cells, which were matched for donor age, and passage number, were either derived from Kearns-Sayre syndrome (KSS) patients, which constitutively carry large amounts of the UV-inducible mitochondrial common deletion, or normal human volunteers (NHF). In the present study we have focused on the analysis of changes that occur in this system within the first four days of culture. We have found that KSS fibroblasts – in comparison to NHF – contracted the gels faster and stronger. This effect was dependent on reactive oxygen species (ROS) as the contraction difference was reduced in an oxygen-deprived atmosphere and in the presence of the antioxidant N-tert-butyl-α-phenylnitrone (PBN), respectively. Gene expression and Western blot analysis revealed significant upregulation of lysyl oxidase (LOX), an enzyme required for crosslinking of collagen fibers, in KSS fibroblasts. Treatment with the specific LOX inhibitor β-aminopropionitrile (BAPN) decreased the contraction difference between KSS and NHF equivalents to a similar degree as PBN, and both BAPN and PBN diminished LOX activity. These data suggest a causal relationship between mtDNA deletions, ROS production, and increased LOX activity, which then leads to increased contraction of collagen gels. They support the concept that mtDNA deletions in human skin fibroblasts lead to functional and structural alterations of the skin. Accordingly, increased LOX expression was also observed *in vivo* in photoaged human and mouse skin.