EVIDENCE OF ALTERED REDOX BALANCE AND ENERGY METABOLISM IN XPA-DEFECTIVE HUMAN CELLS

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There is mounting evidence that DNA repair/DNA damage response defects are associated with increased intracellular ROS and accumulation of oxidatively generated DNA damage (D'Errico 2013). We have recently shown that also the inactivation of the nucleotide excision repair Xeroderma pigmentosum A (XP-A) gene leads to accumulation of 8-oxoguanine in nuclear DNA likely accounting for the hypersensitivity of XP-A human primary fibroblasts to oxidizing agents (Parlanti 2012).

Here, we show that XP-A defective human cells have an altered redox balance. The steady-state ROS levels were significantly higher both in primary fibroblasts from XP-A donors and in XPA-silenced human cells as compared to normal. This alteration was associated with a shift toward a glycolytic metabolism, as analysed by ^{1}H-NMR. and with a lower levels of endogenous ATP.

To monitor the functionality of mitochondria, cells were grown in the presence of rotenone, a specific inhibitor of the mitochondrial complex 1, and live-cell imaging was conducted by using tetramethylrhodamine ethyl ester (TMRE) as a probe for mitochondrial membrane potential. More active mitochondria were identified in XP-A cells as compared to normal cells.

Moreover, XP-A cells showed increased genetic instability following induction of oxidatively generated DNA damage, as measured by micronucleus frequency.

On the basis of these findings we envisage a model where the lack of XPA, by leading to accumulation of oxidatively generated DNA damage, activates the oxidative stress response with subsequent ROS production. This mechanism might contribute to the increased skin cancer risk and neurodegeneration typical of XP-A patients.