APOPTOSIS OF FANCONI ANEMIA CELLS INDUCED BY MITOMYCIN C IS RELATED TO THE MITOCHONDRIAL RESPIRATORY STATE.

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Fanconi anemia (FA) is a rare, multi-genic disorder characterized by hematological abnormalities, developmental defects and increased cancer susceptibility. FA cells are hypersensitive to oxidative stress and cross-linking agents, such as mitomycin C (MMC). However, the relationship between the sensitivity of FA cells to MMC and the capacity of this drug to induce oxidative stress or alterations in the mitochondrial function of these cells have not been convincingly demonstrated. Basal, uncoupled (2 μg/mL oligomycin) or total respiration (2 μM FCCP) showed that all these respiratory states were increased, at least two fold, after FA cell treatment with MMC. However, the uncoupled respiration was higher in control cells (wild-type phenotype - HSC536 + FANCC) than in FA cells. The anti-oxidant agent Trolox did not alter the uncoupled respiration rate nor modify NF-?B (a marker of oxidative stress) activation both in control and FA cells. Trolox delays the loss of FA cell viability induced by MMC. The FA cell death promoted by MMC involves the apoptotic pathways as evaluated by fluorescence microscopy of ethidium bromide and acridine orange. These results indicate that oxidative stress and the apoptotic cell death induced by MMC in FA cells may be related to the distinct mitochondrial membrane permeability.