Autophagy, senescence and mitochondrial content in nucleotide excision repair deficient cells treated with doxorubicin

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Doxorubicin (DOX) is an important agent in cancer therapy and its mechanism of action includes topoisomerase II-poisoning, free radicals release and DNA adducts formation. The nucleotide excision repair (NER) participates in the removal of lesions that distort the double helix of DNA induced by UV and chemicals. Cell lines deficient in NER are more sensitive to anthracyclines, however little is known about the cellular processes that permit cell survival after treatment with these drugs. In this work we verified the cellular response to DOX induced lesions in human fibroblast cell lines proficient (MRC5) and deficient in NER (CSB, XPA, and XPD) after 72h DOX treatment. The results indicate that cell lines deficient in NER are more sensitive to DOX and die in a dose dependent manner mainly by apoptosis. A proficient MRC5 and XPA deficient cell lines showed a higher percentage of cells in G2/M phase, an increased number of hours required for doubling, increase in senescence markers and in acridine orange staining, indicating autophagy process induction after DOX treatment, while CSB and XPD do not present none of these characteristics. XPD cells also presented a lower mitochondrial content than MRC5, and this profile seems to be recovered in XP cells complemented by the wild type XPD cDNA. An important clue comes from recent studies linking autophagy with the onset of senescence. Thus, autophagy and senescence may be part of the same physiological process. We can infer that efficient NER following treatment with DOX seems to be essential for cell survival. On the other hand, recruitment of NER pathway factors seems to be necessary for induction of specific cellular responses such as autophagy and senescence.

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