ENDOGENOUS DNA DAMAGE AND DNA REPAIR DEFICIENCY IN DOWN SYNDROME FIBROBLASTS

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DNA damage has been suggested to significantly contribute to the etiology of several human diseases, including genetic diseases and tumors. In particular, DNA damage and deficiency in DNA repair have been associated with diseases, such as Xeroderma Pigmentosum (XP), Cockaine syndrome (CS), Trichothiodystrophy (TTD), and other genetic diseases. In the last years, defects in DNA repair have also been called into question for age-related diseases, such as Alzheimer disease (AD), Parkinson disease (PD), and Down syndrome (DS). Increased accumulation of DNA lesions, and specifically those produced by oxidative damage, possiblly in association with defects in DNA repair, have been indicated as one of the factors involved in the etiology of these syndromes. We are studying the involvement of DNA damage and its repair in some aspect of DS because these patients are prone to develop tumors, particularly some leukemias, in addition to aging early. In this work we have investigated the presence of endogenous DNA damage and the repair of oxidative lesions by the base excision repair (BER) mechanism in fetal, as well as adult dermal fibroblasts obtained from DS patients.

The results have shown that DS fibroblasts are characterized by signs of endogenous DNA damage, and activation of the DNA damage response, as evidenced by the appearance of the phosphorylated form of histone H2AX (g-H2AX), increased levels of p53, and by Thr68 Chk2 protein phosphorylation. The presence of cells showing a typical comet tail, when tested by the Comet assay, in DS cell cultures grown under normal conditions, further supported this conclusion. In addition, activation of the DNA damage response pathway was indicated by the increase in the number of cells entering a senescent state, as determined by the increase in beta-galactosidase. The cloning efficiency after oxidative DNA damage induced by potassium bromate ($KBrO_3$), indicated that both fetal and adult DS fibroblasts were more sensitive to this type of lesions, than cells from normal donors. These results suggest a deficiency in the BER process, because DS cells did not show recovery of DNA damage induced by $KBrO_3$, as assessed by the Comet test. An increase in the chromatin-bound form of XRCC1 in DS fibroblasts, observed both in the absence and in the presence of DNA damage, pointed to a possible cause of DNA repair defects. These results suggest that DS cells are prone to genome instability which may lead to cell senescence, and ultimately to carcinogenesis, not only because of an increase in DNA damage, but also because of defects in DNA repair.