THE ROLE OF P53 IN DNA REPAIR DEFICIENT SYNDROMES HYPERSENSITIVE TO UV LIGHT

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The ultraviolet (UV) component of sunlight is known to induce lesions on genomic DNA. Among the many responses of human cells following genotoxic stress is the nuclear accumulation of p53, a tumor suppressor protein, which plays an essential role in cell cycle control. There exist three distinct human hereditary diseases hypersensitive to UV light, xeroderma pigmentosum (XP), Trichothiodystrophy (TTD) and Cockayne's syndrome (CS) that carry mutations in genes involved in nucleotide excision repair (NER) and RNA transcrption. We have analysed cells from these syndromes and have shown that the lesions localized on the transcribed strand of active genes are responsible for the prolonged accumulation of the p53 protein in human cell nuclei following UV induced damage. This protein protects the cells from the deleterious effects of UV. In fact, p53 is a transcriptional factor whose accumulation induces the expression of genes such as *WAF1* and *GADD45*. The products of these genes inhibit the replication of damaged DNA and stimulate its repair. If the repair is not complete, replication of UV damaged DNA transforms the lesions into mutations. These mutations may be responsible of oncogene activation and tumor suppressor gene inactivation which promote the tumoral transformation of cells. Inactivation of the p53 tumor suppressor gene by solar UVB induced mutations is an early and essential step of skin carcinogenesis and may promote genetic instability in cutaneous cells which lead to skin tumor development. The carcinogenic effects of UV light are manifested by the highly cancer prone XP patients where we have shown that over 70% of the cutaneous carcinomas carry significant alterations of the p53 gene. All mutations are targeted at dipyrimidine sites, the hot spots for UV induced lesions and the majority are GC→AT transitions. Most significantly, over 70% of these are CC>TT tandem mutations considered to be the veritable signature of UV induced lesions. The majority of the mutations are due to the presence of unrepaired lesions remaining on the the non-transcribed strand of the p53 gene in the XP tumors. Indeed, this is the first demonstration of the existence of preferential repair in man.