VIII. ABSTRACT

The DNA integrity is always threatened by the damage effects of physical and chemical agents that could jeopardy its function. The nucleotide excision repair (NER) is one of the most known and flexible mechanisms of DNA repair. This mechanism can recognize and remove DNA double-helix distortion, including the cyclobutane pyrimidine dimers (CPDs) and the pyrimidine-pyrimidone (6-4) photoproduct, promoted by ultraviolet light (UV). The human syndrome xeroderma pigmentosum (XP) is clinically characterized chiefly by the early onset of severe photosensitivity of the exposed regions of the skin, a very high incidence of skin cancers and frequent neurological abnormalities. The *xpa* gene seems to be involved during the UV damage recognition, in both global genome repair (GGR) and transcription-coupled repair (TCR). This gene modulation may modify the DNA repair rate in the cell genome, providing valuable contribution to the NER understanding and other DNA repair pathways. However, the complete inactivation or even the attenuation of the XPA transcript was not possible, mainly because of the low abundance mRNA per cell and the high stability of the XPA protein. The controlled expression of the cDNA *xpa* in XP12RO deficient cells was achieved through the transfection of a muristerone-A inducible vector, pINXA. The INXA15M clone shows good induction of the XPA protein and total complementation of XP12RO cells deficiency. Small quantities of the XPA protein do not interfere in the cellular UV sensitivity and the DNA repair activity in the global genome. Nevertheless, a higher number of cells in the apoptotic process were detected in short periods of time after UV light when compared to normal cells (HeLa). The adenovirus vector carrying the cDNA *xpa* (AdyXPA) can efficiently complement XPA patients' fibroblast cells. In spite of the short period of the transgene expression and the known imunological reaction caused by adenovirus, this

vector represents a potential tool for gene complementation diagnostic and gene correction in XP patients.