INVOLVEMENT OF THE p53/p21$^{WAF1/CIP1}$ SYSTEM IN THE RESPONSE OF HUMAN CANCER CELLS TO DOXORUBICIN TREATMENT

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The development of drug resistance is a major obstacle to the effectiveness of chemotherapeutic treatment of human tumors with cytotoxic agents, including the anthracycline antibiotic doxorubicin. Doxorubicin is clinically used for the treatment of a wide variety of cancers, such as acute myeloid leukaemia and a number of solid tumors.
In recent years, the preclinical observation that effective chemotherapeutic drugs are able to induce apoptosis in tumor cells has attracted major pharmacological interest on this mode of cell death, and the hypothesis that induction of apoptosis might be a critical determinant of tumor cell sensitivity has gained increasing popularity. A number of molecular alterations associated with transformation and/or tumor progression may be implicated in the regulation of cell death pathways and in the development of drug resistance. Experimental evidence indicates that mutations/deletions in the *p53* gene may lead to failure of anticancer therapy. Although a role of p53 in apoptosis is well established, the relationship between p53, and its downstream effectors, and drug sensitivity remains controversial.
The aims of this study are:

- to understand the role of the p53/p21 system in the response of human cancer cells to doxorubicin treatment
- to improve the therapeutic index of doxorubicin by modulation of p53 and p21 protein levels.

We first investigated the relationship between p53 and p21 protein levels and the cytotoxic effect of doxorubicin in human breast and colon cancer cell lines characterized by different *p53* status. We have also evaluated the effects of doxorubicin on cell lines obtained by transfection of cells with a pCMVneo-E6 plasmid containing the HPV16-E6 human gene, leading to p53 degradation. Our results indicate that cells lacking p53 function and p53-dependent upregulation of p21 expression are less responsive to drug treatment, in contrast with cells maintaining the ability to upregulate p21 by p53-independent pathways upon exposure to doxorubicin. These observation suggest that sensitivity to doxorubicin in the cell lines tested may be associated to the ability of the cells to up-regulate p21 protein expression.