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The Yeast as an Alternative Experimental Model in the Study of Anticancer Drugs

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The difficulties encountered in cancer therapy and research have led to the use of alternative experimental models in order to study the processes of cell cycle and division, the mechanisms of action of anticancer drugs and the phenomenon of multi-drug resistance. This work is aiming at presenting the experimental results regarding the action of antineoplastic agents in the cell cycle under physiological and stress conditions in lower eukaryotes. The ultimate objective is to formulate hypotheses regarding cellular mechanisms, the investigation of which may facilitate the comprehension of corresponding mechanisms in higher eukaryotic cells, with particular emphasis in the field of cancer. *Saccharomyces cerevisiae* was used as the experimental microorganism throughout the studies presented here. Its universal acceptance as a research model originates from the significant homology of its genes to those of higher eukaryotes, the structural and functional similarities to its phylogenetically distant relatives, its rapid growth and the potential to obtain reliable results following genetic and pharmacological manipulations on yeast cells. The preliminary investigation of the effects of various anticancer agents on a number of wild-type yeast strains demonstrated that the most sensitive strain to this group of drugs was *Saccharomyces cerevisiae* ATCC 2366, which was therefore selected as the strain of choice for all further experiments. The yeast response to the anticancer agents has been shown to be as follows: all the agents apart from the chromatin function inhibitors induced cytotoxic effects on yeast. Specifically, amongst others 5-fluorouracil (5-FU) and cisplatin induced dose- and time-dependant inhibition of growth, while doxorubicin and tamoxifen produced cytocidal effects. The inhibitory action of *m*-amsacrine was exposed only after co-administration of verapamil, supporting the existence in yeast of a mechanism, which drives anticancer drugs out of the cell, similar to the one involving p-glycoprotein in higher eukaryotes. This result does not exclude, however, the significance of K^+ channels and membrane electrochemical properties in the phenomenon of drug resistance in yeast. A large number of anticancer drugs including 5-FU, methotrexate, mitomycin-C, bleomycin, cisplatin, hydroxyurea, carboplatin and dacarbazine induced morphological alterations in yeast, suggesting a possible action of these drugs in gene transcription/regulation. Since the presence of the cell wall has been shown to prevent drug entry into the intracellular space, the effects of vinca alcaloids, paclitaxel and etoposide have been studied in yeast spheroplasts. The results have shown that even after the enzymatic removal of the cell wall, the yeast remained resistant to these agents. Finally, it is interesting to note the sub-toxic doses of 5-FU, methotrexate, cisplatin, bleomycin, mitomycin-C and camptothecin-11 induced a response similar to that observed following mild heat stress. The inhibition of this response by cycloheximide implies the involvement of protein cellular components in the induction of pharmacological stress. In conclusion, the evaluation of the results shows that even though the action of anticancer agents in yeast exhibits significant differentiation, the use of this microorganism as an experimental model might contribute to the study of particular mechanisms present in higher eukaryotic cells.