8 Abstract

The knowledge of the influence of genetic lesions in colorectal carcinoma cells on sensitivity to chemotherapeutic agents would allow a better characterization of their effects and therefore lead to an improved treatment of patients with colorectal tumors.

For that reason the influence of p21 expression, a p53 mutation and a mismatch repair defect was examined.

The used short-term assay (MTT test) showed a higher sensitivity of cells expressing high p21 after treatment with 5-FU. In the used long-term assay (clonogenic assay), however, this correlation could be excluded for 5-FU as well as for CPT-11.

Consequently, this part of the research showed the necessity to use different methods to determine resistance of tumor cells to chemotherapeutic agents. The clonogenic assay appears to be the better method to predict long-term effects.

For further analysis the clonogenic assay was used. A p53 mutation led to higher resistance to 5-FU and UCN-01 in MMR^+ cell lines and had no influence on the sensitivity to CPT-11.

A defect mismatch repair system enhanced resistance to 5-FU and UCN-01 in $p53^{wt}$ cell lines, but there was no effect on the sensitivity to CPT-11. The different response of cells after 5-FU treatment dependant on p53 and MMR status could not be explained by a difference in apoptosis or senescence of the cells. Therefore, single genetic alterations were not sufficient to explain the response of tumors to therapy.

Furthermore, the synergism of UCN-01 in combination with cytotoxic agents was examined. The combination of UCN-01 increased the cytotoxicity of 5-FU and CPT-11 in $p53^{mut}$ cell lines. In $p53^{wt}$ cells a protective effect was described in combination with UCN-01, while in the established cell lines of normal mucosa an increase in cytotoxicity has been observed. With regard to the therapeutic use of UCN-01 in combination with other chemotherapeutic agents, further research appears to be useful for the understanding of the exact molecular mechanisms.