THE ANTITUMOR ACTIVITIES OF CURCUMIN AND OF ITS NOVEL ISOXAZOLE ANALOGUE MR 39 ARE NOT HAMPERED BY THE MULTIDRUG RESISTANT CONDITION OF TUMOR CELLS EXPRESSING BOTH P-GLYCOPROTEIN AND DIFFERENT INHIBITORY OF APOPTOSIS PROTEINS (IAPS)

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There is an increasing evidence that the dietary polyphenol curcumin (CUR) is endowed with interesting antitumor properties but not much is known about its activity on chemoresistant cells. We have examined its effects in HL-60 myeloid leukaemia, MCF-7 breast cancer, their multidrug resistant (MDR) counterparts HL-60R and MCF-7R as well as in the hepatocellular carcinoma HA22T/VGH cell line. We have previously shown that HL-60R, MCF-7R and HA22T/VGH over-express P-glycoprotein (P-gp) and different members of the IAP (Inhibitory of Apoptosis Proteins) family; further, in contrast to MCF-7, MCF-7R is estrogen-independent owing to the lack of ERα. Through analyses of cell growth (MTS and BrdU incorporation assays) and of cell death (flow cytometry evaluation of PI-stained DNA and of annexin V binding) we have observed that the antitumor activities of CUR and of its, more potent (more than two-fold), novel isoxazole analogue MR 39 are at least equivalent in the MDR cell lines compared to the parental ones. In addition, CUR and MR 39 exhibited substantial antitumor effects in the HA22T/VGH cells.
Evaluations by RT-PCR of the expression of a series of proliferation- and survival-related genes in MCF-7 and MCF-7R showed that CUR and MR 39 determine early (at 4 and 8 h) modifications in the RNAm levels of some of them; interestingly, however, these changes were mostly different (i.e., represented by decreases in COX-2 and IAPs in MCF-7R versus reductions in Bcl-2 and Bcl-X_L and increases in Bcl-X_S/Bcl-X_L ratio in MCF-7) in the two cell lines. To explain these findings, one might put forth, beside the involvement of ERα, the role of other transcription factors, like NF-kB and STAT-3, which might be differently expressed in MCF-7 and MCF-7R. However, the weak nuclear levels of activated NF-kB and STAT-3 exhibited by MCF-7 were only slightly, though significantly, elevated in MCF-7R: moreover, CUR and MR 39 did not cause changes in the activation of the two factors which could account for their different effects on gene expression in the two cell lines and alternative explanations have to investigated. Overall, these data underline in a promising way that CUR antitumor activity is not hampered by P-gp and by other critical factors, including the IAPs, able to inhibit growth inhibition and cell death from conventional anticancer agents; remarkably, the agent appeared to modify its molecular effects according to diverse gene expression patterns existing in the drug resistant and parental breast cancer cells. The data on MR 39 show also that the structure and properties of CUR may form the basis for the development of antitumor compounds more effective against both chemosensitive and drug resistant cells.