Drug resistance in cancer: from biology to molecular targets and drugs

ABSTRACTS
Quercetin enhances 5-fluorouracil-induced apoptosis in MSI colorectal cancer cells through p53 modulation

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Colorectal tumors (CRC) with microsatellite instability (MSI) show resistance to chemotherapy with 5-fluorouracil (5-FU), the most widely used pharmacological drug for CRC treatment. The aims of this study were to test the ability of quercetin (Q) and luteolin (L) to increase sensitivity of MSI CRC cells to 5-FU and characterize the dependence of the effects on cells' p53 status.

Two MSI human CRC-derived cell lines were used, CO115 wild-type (wt) for p53 and HCT116 that harbors a p53 mutation. Apoptosis induction in these cells by 5-FU, Q and L alone and in combinations were evaluated by TUNEL and western blotting. The dependence on p53 of the effects was confirmed by small interfering RNA (siRNA) in CO115 cells and in MSI HCT116 wt and p53 knockout cells.

CO115 p53 wt cells are more sensitive to 5-FU than the p53 mutated HCT116. The combination treatment of 5-FU with L and Q increased apoptosis with a significant effect for Q in CO115. Both flavonoids increased p53 expression in both cell lines, an effect particularly remarkable for Q. The significant apoptotic enhancement in CO115 incubated with Q plus 5-FU involved the activation of the apoptotic mitochondrial pathway. Importantly, knockdown of p53 by siRNA in CO115 cells and p53 knockout in HCT116 cells totally abrogated apoptosis induction, demonstrating the dependence of the effect on p53 modulation by Q.

This study suggests the potential applicability of these phytochemicals for enhancement 5-FU efficiency in MSI CRC therapy, especially Q in p53 wt tumors.

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