Ha-ras overexpression mediated cell apoptosis in the presence of 5 fluorouracil

邱文祥

Tseng;Ya-Shih.;;Tseng;Ching-Cherng.;Chiu;Allen. W.;;;

摘要

Abstract

By using a mouse NIH3T3 derivate designed 7-4 harboring the inducible Ha-ras oncogene, we demonstrated the close relationship between Ha-ras expression level and sensitization of 5-flurouracil (5-FU)-treated cells. Further studies revealed that the cells susceptible to 5-FU treatment died of apoptosis, which was demonstrated by caspase-3 activation, loss of mitochondria membrane potential (MMP), and DNA fragmentation. The 7-4 cells coexpressing dominant negative Ras (RasAsn17), dominant negative Raf-1 (Raf-1CB4), Bcl-2, or active form of phosphatidylinositol 3-kinase (PI3K) became resistant to 5-FU, and apoptosis was prevented. In contrast, the cells coexpressing dominant negative Rac 1 (Rac1Asn17) or dominant negative Rho A (RhoAAsn19) showed no change of sensitivity to 5-FU. These results indicate that Ras, Bcl-2, as well as Raf-1 and PI3K pathways play pivotal roles in 5-FU-induced apoptosis under Ha-ras-overexpressed condition. Aberrant levels of cyclin E and p21Cip/WAF-1 expression as well as Cdc 2 phosphorylation at Tyrosine 15 suggest that perturbation of G1/S and G2/M transitions in cell cycle might be responsible for 5-FU triggered apoptosis. Sensitization of Ha-ras-related cells to 5-FU was also demonstrated in human bladder cancer cells. Through understanding the mechanism of 5-FU induced apoptosis in tumor cells, a new direction toward the treatment of Ha-ras oncogene-related cancers with 5-FU at more optimal dosages is possible and combinational therapy with other drugs that suppress PI3K and Bcl-2 activities can also be considered.