

Molecular mechanisms of G0/G1 cell cycle arrest and apoptosis induced by terfenadine in human cancer cells

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摘要

Abstract

Terfenadine (TF), a highly potent histamine H1 receptor antagonist, has been shown to exert no significant central nervous system side effects in clinically effective doses. In this study, we demonstrated that TF induced significant growth inhibition of human cancer cells, including Hep G2, HT 29, and COLO 205 cells, through induction of G(0)/G(1) phase cell-cycle arrest. The minimal dose of TF induced significant G(0)/G(1) arrest in these cells was 1-3 microM. The protein levels of p53, p21/Cip1, and p27/Kip1 were significantly elevated, whereas the kinase activities of cyclin-dependent kinase 2 (CDK2) and CDK4 were inhibited simultaneously in the TF-treated cells. On the other hand, significant apoptosis, but not G(0)/G(1) arrest, was induced in the HL 60 (p53-null) or Hep 3B (with deleted p53) cells when treated with TF (3-5 microM). To clarify the roles of p21/Cip1 and p27/Kip1 protein expression, which was involved in G(0)/G(1) arrest and apoptosis induced by TF in human cancer cells, antisense oligodeoxynucleotides (ODNs) specific to p21/Cip1 and p27/Kip1 were used, and the expression of the p21/Cip1 and p27/Kip1 were monitored by immunoblotting analysis. Our data demonstrated that the percentage of the apoptotic cells detected by annexin V/PI analysis in the TF-treated group was clearly attenuated by pretreatment with p27/Kip1-specific ODNs. These results indicated that p27/Kip1 (but not p21/Cip1) protein indeed played a critical role in the TF-induced apoptosis. We also demonstrated that the TF-induced G(0)/G(1) cell-cycle arrest effect was not reversed by TF removal, and this growth inhibition lasted for at least 7 d. Importantly, the occurrence of apoptosis and cell growth arrest was not observed in the TF-treated normal human fibroblast, even at a dose as high as 25 microM. Our study showed the molecular mechanisms for TF-induced cell growth inhibition and the occurrence of apoptosis in

human cancer cells.

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