Checkpoint kinase 1-mediated phosphorylation of Cdc25C and Bad proteins are involved in antitumor effects of loratadine-induced G2/M phase cell cycle arrest and apoptosis.

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摘要

Abstract

In this study, we first demonstrated that loratadine (LOR), a promising world widely used oral anti-histamine, effectively inhibits growth of tumors derived from human colon cancer cells (COLO 205) in an in vivo setting. In vitro study demonstrated that the anti-tumor effects of LOR in COLO 205 cells were mediated by causing G(2)/M phase cell growth cycle arrest and caspase 9-mediated apoptosis. Cell-cycle arrest induced by LOR (75 microM, 24 h) was associated with a significant decrease in protein levels of cyclin B1, cell division cycle (Cdc) 25B, and Cdc25C, leading to accumulation of Tyr-15-phosphorylated Cdc2 (inactive form). Interestingly, LOR (75 microM, for 4 h) treatment also resulted in a rapid and sustained phosphorylation of Cdc25C at Ser-216, leading to its translocation from the nucleus to the cytoplasm because of increased binding with 14-3-3. We further demonstrated that the LOR-induced Cdc25C (Ser-216) phosphorylation was blocked in the presence of checkpoint kinase 1 (Chk1) specific inhibitor (SB-218078). The cells treated with LOR in the presence of Chk1 specific inhibitor (SB-218078) were then released from G(2)/M arrest into apoptosis. These results implied that Chk1-mediated phosphorylation of Cdc25C plays a major role in response to LOR-mediated G(2)/M arrest. Although the Chk1-mediated cell growth arrest in response to DNA damage is well documented, our results presented in this study was the first report to describe the Chk1-mediated G(2)/M cell-cycle arrest by the histamine H1 antagonist, LOR.

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