Griseofulvin potentiates antitumorigenesis effects of nocodazole through induction of apoptosis and G2/M cell cycle arrest in human colorectal cancer cells

林建煌
Ho YS;Dun JS;Jeng JH;Wang YJ;Liang YC;Lin CH;Tseng CJ;Yu CF;Chen RJ and Lin JK

Abstract

In this study, we demonstrate that apoptosis and G2/M cell cycle arrest were easily induced by treatment with the oral-antifungal agent, griseofulvin (GF). The mechanisms of GF-induced G2/M arrest were characterized as (a) induction of abnormal mitotic spindle formation, (b) elevation of cyclin B1/cdc2 kinase activity and (c) down-regulation of myt-1 protein expression. On the other hand, caspase 3 activation, Bcl-2 hyperphosphorylation and inhibition of the normal function of Bcl-2 associated with Bax were demonstrated to be the mechanisms of GF-induced apoptosis. DNA fragmentation and flow cytometry analyses demonstrated that combined treatment of GF with the cancer chemotherapeutic agent, nocodazole (ND), strongly potentiates the apoptotic effect and arrest of the G2/M cell cycle in 5 types of human cancer cells, but not in normal human keratinocytes (#76 KhGH). The combined treatment of GF and ND triggered the polymerization of purified tubulin in HT 29 but not in #76 KhGH cells. To further confirm these observations, the therapeutic efficacy was further examined in vivo by treating athymic mice bearing COLO 205 tumor xenografts, with GF (50 mg/kg), ND (5 mg/kg) or GF + ND. Combined treatment of GF and ND significantly enhanced the effect of ND, and led to cessation of tumor growth. These results suggest that chemotherapeutic agents (such as ND) administered in the presence of GF might provide a novel therapy for colorectal cancer.