NF-κB pathway is involved in griseofulvin-induced G2/M arrest and apoptosis in HL60 cells

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摘要

Abstract

Griseofulvin (GF), an oral antifungal agent, has been shown to exert antitumorigenesis effect through G2/M cell cycle arrest in colon cancer cells. But the underlying mechanisms remained obscure. The purpose of this study is to test the cytotoxic effect of GF on HL-60 and HT-29 cells and elucidate its underlying molecular pathways. Dose-dependent and time-course studies by flow cytometry demonstrated that 30 to 60 microM GF significantly induced G2/M arrest and to a less extend, apoptosis, in HL-60 cells. In contrast, only G2/M arrest was observed in HT-29 cells under similar condition. Pretreatment of 30 microM TPCK, a serine protease inhibitor, completely reversed GF-induced G2/M cell cycle arrest and apoptosis in HL-60 cells but not in HT-29 cells. The GF-induced G2/M arrest in HL-60 cells is reversible. Using EMSA and super-shift analysis, we demonstrated that GF stimulated NF-kappaB binding activity in HL-60 cells, which was completely inhibited by pretreatment of TPCK. Treatment of HL-60 with 30 microM GF activated JNK but not ERK or p38 MAPK and subsequently resulted in phosphorylation of Bcl-2. Pretreatment of TPCK to HL-60 cells blocked the GF-induced Bcl-2 phosphorylation but not JNK activation. Time course study demonstrated that activation of cdc-2 kinase activity by GF correlated with Bcl-2 phosphorylation. Taken together, our results suggest that activation of NF-kappaB pathway with cdc-2 activation and phosphorylation of Bcl-2 might be involved in G2/M cell cycle arrest in HL-60 cells.