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ブナシメジ由来 Hypsiziprenol A_9 による cAMP 経路の抑制を介した HL-60 細胞のアポトーシス誘導

Apoptosis induced by Hypsiziprenol A_9 from *Hypsizigus marmoreus via* down-modulation of cAMP signaling pathways in HL-60 cells

We have reported previously that ethyl acetate-extracts from the fruiting body of a Japanese edible mushroom,Buna-shimeji (*Hypsizigus marmoreus*), exhibited strong anti-tumor activities against tumor-bearing mice,and that the main active substance of its extracts was identified as a polyterpene, Hypsiziprenol A_9. Hypsizipreno1 A_9 inhibited the growth of various human cancer cell lines. However, its antitumor mechanism has not been studied in detail. To elucidate its mechanism, we examined Hypsiziprenol A_9-induced apoptosis in human promyelocytic leukemia HL-60 cells. Hypsiziprenol A_9 strongly inhibited the growth of HL-60 cells in a dose-dependent manner. Formation of apoptotic bodies was observed within 4 hr of Hypsiziprenol A_9 treatment. Pan-caspase inhibitor (Z-VAD-FMK) attenuated anti-proliferation effect of Hypsiziprenol A_9. Hypsiziprenol A_9-induced apoptosis was strongly inhibited by cAMP analogue (DBcAMP) or by cAMP-eleveting agents (Forskolin and IBMX), whereas p38 MAPK inhibitor (SB203580) , JNK inhibitor (SP600125) and calcium chelators (EGTA,BAPTA-AM) had no effect. Thus,these results suggest that Hypsiziprenol A_9 inhibits the growth of HL-60 cells by inducing apoptosis *via* the down-modulation of cAMP signaling pathway.