3,3'-Diindolylmethane suppresses the growth of gastric cancer cells via activation of the Hippo signaling pathway.

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Abstract

Recent studies have revealed that 3,3-diindolylmethane (DIM) has antitumor effects in both in vivo and in vitro tumor models. However, the biological function of DIM in human gastric cancer cells is unknown. Genetic and biological studies have confirmed the importance of the novel Hippo tumor-suppressor pathway in regulating cell proliferation, apoptosis, organ size and tumorigenesis in mammals. Thus, the purpose of this study was to investigate the cytotoxic effects of DIM in human gastric cancer cells and to elucidate whether DIM induces cell death by activating the Hippo signaling pathway. Two human gastric cancer cell lines (SNU-1 and SNU-484) were used to investigate the DIM response. DIM significantly inhibited the proliferation of human gastric cancer cells in a dose-dependent manner. The percentage of G1 phase cells increased 24 h following DIM treatment. DIM reduced CDK2, CDK4, CDK6 and cyclin D1 protein levels, while increasing p53 protein levels. DIM induced the levels of cleaved poly(ADP-ribose) polymerase, cleaved-caspase-9, and diminished pro-caspase-3 protein production. In addition, DIM increased pLATS1, Mob1, pMob1, pYAP and Ras association domain family 1 (RASSF1) protein levels and reduced Yap protein production levels. DIM stimulated the binding of RASSF1 with the Mst1/2-LATS1-Mob1 complex, promoting an active Hippo signaling pathway and favoring YAP phosphorylation (pYAP) that inactivates cell proliferation. Furthermore, DIM inhibited the growth of human gastric tumors in a xenograft mouse model. These results indicate that DIM suppresses the growth of gastric cancer cells by activating the Hippo signaling pathway.

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