Ácido betulínico induz apoptose no câncer humano via liberação mitocondrial de citocromo c

Betulin induces mitochondrial cytochrome c release associated apoptosis in human cancer cells.

Li Y, He K, Huang Y, Zheng D, Gao C, Cui L, Jin YH.

Source
Key Laboratory for Molecular Enzymology, Engineering of the Ministry of Education, Jilin University, Changchun, China.

Abstract
We examined whether betulin, a naturally abundant compound, has anticancer functions in human cancer cells. The results showed that betulin significantly inhibited cell viability in cervix carcinoma HeLa cells, hepatoma HepG2 cells, lung adenocarcinoma A549 cells, and breast cancer MCF-7 cells with IC(50) values ranging from 10 to 15 microg/mL. While betulin exhibited only moderate anticancer activity in other human cancer cells such as hepatoma SK-HEP-1 cells, prostate carcinoma PC-3, and lung carcinoma NCI-H460, with IC(50) values ranging from 20 to 60 microg/mL, it showed minor growth inhibition in human erythroleukemia K562 cells (IC(50) > 100 microg/mL). We further investigated the mechanism of anticancer activity by betulin, using HeLa cells as an experimental model. Betulin (10 microg/mL) induces apoptotic cell death, as evidenced by morphological characteristics such as membrane phosphatidylserine translocation, nuclear condensation/fragmentation, and apoptotic body formation. A kinetics analysis showed that the depolarization of mitochondrial membrane potential and the release of mitochondrial cytochrome c occurred as early as 30 min after treatment with betulin. Betulin, unlike its chemical derivative betulinic acid, did not directly trigger mitochondrial cytochrome c release in isolated mitochondria. Importantly, Bax and Bak were rapidly translocated to the mitochondria 30 min after betulin treatment. The sequential activation of caspase-9 and caspase-3/7 and the cleavage of poly(ADP-ribose) polymerase (PARP) were observed behind those mitochondrial events. Furthermore, specific downregulation of either caspase-9, Bax, or Bak by siRNA effectively reduced PARP cleavage and caspase-3 activation. Taken together, the lines of evidence demonstrate that betulin triggers apoptosis of human cancer cells through the intrinsic apoptotic pathway.
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