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Isoobtusilactone A induces cell cycle arrest and apoptosis through reactive oxygen species /apoptosis signal-regulating kinase 1 signaling pathway in human breast cancer cells

Po-Lin Kuo[1], Chung-Yi Chen[2], Ya-Ling Hsu[1]

[1]Cell Biology Laboratory, Department of Biotechnology, Chia-Nan University of Pharmacy and Science, Tainan, Taiwan
[2]Basic Medical Science Education Center, Fooyin University, Kaohsiung, Taiwan
Correspondence e-mail address: kuopolin@seed.net.tw

Abstract

This study is the first to investigate the anticancer effect of isoobtusilactone A (IOA) in two human breast cancer cell lines, MCF-7 and MDA-MB-231. IOA exhibited effective cell growth inhibition by inducing cancer cells to undergo G2/M phase arrest and apoptosis. Further investigation revealed that IOA's inhibition of cell growth was also evident in a nude mice model. Cell cycle blockade was associated with increased levels of p21, and reduced amounts of cyclinB1, cyclinA, cdc2 and cdc25C. IOA also enhanced the levels of inactivated phosphorylated cdc2 and cdc25C. IOA triggered the mitochondrial apoptotic pathway, as indicated by a change in Bax/Bcl-2 ratios, resulting in mitochondrial membrane potential loss, cytochrome *c* release and caspase-9 activation. We also found that generation of ROS is a critical mediator in IOA-induced cell growth inhibition. Enhancement of ROS by IOA activated apoptosis signal-regulating kinase 1 (ASK1) resulted in increased activation of c-Jun N-terminal kinase and p38. Antioxidants EUK8 and N-acetyl cystenine significantly decreased apoptosis by inhibiting the ASK1 dephosphorylation at Ser967, and subsequently increased the interaction of ASK1 with thioredoxin or 14-3-3 proteins. Moreover, blocking ASK1 by siRNA inhibition completely suppressed IOA-induced apoptosis. Taken together, these results imply a critical role for ROS and ASK1 in IOA's anticancer activity.

Keywords: isoobtusilactone A, apoptosis, ROS