Astragalus membranaceus saponins modulate mTOR and ERK signaling to promote apoptosis through the extrinsic pathway in HT-29 colon cancer cells.


Source

Center for Cancer and Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, PR China.

Abstract

We have previously demonstrated that the total saponins of Astragalus membranaceus (AST) possess potential anti-tumorigenic effects in human colon cancer cells and tumor xenografts. In the present study, the proapoptotic effects of AST were investigated in native and cytokine-induced HT-29 cells to further unveil its mechanism of action. Growth-inhibitory action of AST (60 microg/ml) was demonstrated in native HT-29 cells, which was exaggerated in tumor necrosis factor (TNF) (5 ng/ml)-induced cells. These were accompanied by caspase 3 activation, cleavage of poly(ADP-ribose) polymerase and a subsequent increase in apoptotic cell numbers. Furthermore, activation of procaspase 8 indicates that the extrinsic apoptotic pathway was involved, while cleavage of Bid into t-Bid implicates cross-talk with the intrinsic apoptotic pathway. Alternatively, AST caused S and G2/M phase arrest, while in cytokine-induced cells S phase arrest was predominant. Further adding to our recent suggestion on its correlation with phosphatidylinositol 3-kinase (PI3K)-Akt signaling, we have now
revealed that AST caused overexpression of PTEN and down-regulation of mammalian target of rapamycin (mTOR) expression. Nevertheless, these events were preceded by a decrease in nuclear factor-kappaB (NF-kappaB)/DNA binding activity with continuous ERK 1/2 activation. Some of these effects became more intense in cytokine-induced cells. Our findings in this study suggest that AST induces the extrinsic apoptotic cascade and causes cell cycle arrest in HT-29 cells by modulation of both mTOR and ERK signaling pathways, of which inhibition of NF-kappaB is important in the latter mechanism. Most of the above processes are more pronounced in cytokine-induced cells.

PMID:20664949