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ATP-citrate lyase reduction mediates guggulipid-induced apoptosis in prostate cancer cells

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Guggulipid (GL), herbal extracts from the Indian Ayurvedic plant *Commiphora mukul* (guggul), has been widely used in Asia as cholesterol-lowering agent as well as a variety of ailments including obesity, bone fracture, arthritis, inflammation and cardiovascular disease. In this study, we examined the efficacy and associated mechanisms of GL against prostate cancer cells *in vitro*. Results show that GL significantly decreases cell viability and colony formation in the human prostate cancer cell lines PC3 and LNCaP C4-2 at a dose of 5μM (24 hour treatment), a pharmacologically relevant concentrations standardized to its major active component, z-guggul sterone. Using these two cell lines as a model, we demonstrate that GL induces apoptotic cell death as evidenced by an induction of cleaved poly (ADP-ribose) polymerase (PARP) and caspase 3, sub-G0/G1-DNA fraction and an altered expression profile of BCL-2 family members. Additionally, GL-induced apoptosis is associated with generation of reactive oxygen species (ROS) and reduction of ATP-citrate lyase (ACLY). ACLY inhibition by RNAi or the chemical inhibitor, SB-204990, limits survival of tumor cells. Importantly, GL activates adenosine monophosphate-activated protein kinase (AMPK), a biomarker for cellular energy status. Caspase 3 activation and ROS generation are enhanced in AMPK knockout mouse embryonic fibroblast cells (MEF KO) suggesting that AMPK is involved in GL-induced apoptosis. Overall, the present study indicates that apoptosis induced by GL is via ROS generation, ACLY reduction and AMPK activation in human prostate cancer cells.

Biography

Yajuan Gao is currently working as a Research Associate in Department of Urology, University of Pittsburgh School of Medicine. She received her MD degree from Shenyang Medical College in 1994 and PhD degree from Tongji Medical University in 2001. Her research interest is in the area of prostate cancer chemoprevention by studying dietary bioactive compounds.

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