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AST is a novel anti-carcinogenic regimen against gastrointestinal cancer development with unique molecular targets

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The dried root of *Astragalusmembranaceus* (Radix Astragali) has a long history of medicinal use in Traditional Chinese Medicine as an immunomodulating agent to ameliorate the side effects of cytotoxic antineoplastic drugs. In recent years, we have demonstrated that total *Astragalussaponins* (AST) caused significant growth inhibition and pro-apoptotic effects in human colon adenocarcinoma cells and tumor xenograft, which synergistically worked with conventional chemotherapeutic drug combowhile alleviatingthe associated drug-induced toxicity. Its mechanism of action involved phase-specific cell cycle arrest and exhibited anti-carcinogenic activity in 8 different human cancer cell lines, confirming its universal chemotherapeutic property. By using customized cDNA array, we have revealed that AST increased the gene expression of proangiogenic factors and downregulated the expression of proangiogenic molecules. Besides, genes that are relevant to metastasis and invasion including matrix metallopeptidases and the metastasis associated genes *mta1* and *Twist* were also downregulated. Contribution of AST to the modulation of angiogenesis, tumor invasiveness and metastasis was further confirmed. The anti-metastatic potential of AST could be demonstrated by employing a modified liver metastasis model. We have identified NSAID-activated gene (NAG-1) as a molecular target of AST, which could be correlated with modulation of the upstream PI3K-AST signaling pathway. Other than colorectal cancer cells, AST has also exhibited promising anti-carcinogenic effects in hepatocarcinoma cells by down-regulating expression of the liver tumor marker α-fetoprotein, as well as promoting pro-apoptotic activity through modulation of an ERK-independent NF-κB signaling pathway. Glucose-regulated proteins (GRP) are induced in the cancer microenvironment to promote tumor survival, metastasis and drug resistance.Our findings exemplify that calpains, in particular calpain II, played a permissive role in the modulation of GRP78 and consequent regulation of ER stress-induced apoptosis brought forth by AST.Data obtained from these studies could facilitate future establishment of AST as an effective target-specific chemotherapeutic and adjuvant agent in treating human colorectal and liver cancers, with unique molecular targets such as NAG-1 and calpain.

Biography

Joshua Ko disciplines include pharmacology, toxicology, chemotherapy and gastroenterology. My current research interest and strength focus on the study of the carcinogenesis and pharmacotherapy of gastrointestinal cancers (particularly colon) by using active herbal medicinal compounds, and also on the identification of key molecular drug targets. I have recently explored the potential anti-nociceptive and anti-inflammatory actions of TCM formulations and single herbal drugs in the treatment of cancer pain and inflammation pain. I employ different cell and molecular biology methods, animal models of cancer and pain, with increasing works using proteomics and metabolomics approaches in our current studies. The new ventures in the coming years include research works on micro-RNA and tumor-targeting peptides delivery system.

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