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Guggulsterone decreases proliferation and metastatic behavior of pancreatic cancer cells by modulating JAK/STAT and Src/FAK signaling

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ABSTRACT

Inadequate efficacy, high toxicity and drug resistance associated with existing chemotherapeutic agents mandate a need for novel therapeutic strategies for highly aggressive Pancreatic Cancer (PC). Guggulsterone (GS) exhibits potent anti-proliferative effects against various cancer cells and has emerged as an attractive candidate for use in complementary or preventive cancer therapies. However, the knowledge regarding the therapeutic potential of GS in PC is still limited and needs to be explored. We studied the effect of GS on PC cell growth, motility and invasion and elucidated the molecular mechanisms associated with its anti-tumor effects. Treatment of Capan1 and CD18/HPAF PC cells with GS resulted in dose- and time-dependent growth inhibition and decreased colony formation. Further, GS treatment induced apoptosis and cell cycle arrest as assessed by Annexin-V assay and FACS analysis. Increased apoptosis following GS treatment was accompanied with Bad dephosphorylation and its translocation to the mitochondria, increased Caspase-3 activation, decreased Cyclin D1, Bcl-2 and xIAP expression. Additionally, GS treatment decreased motility and invasion of PC cells by disrupting cytoskeletal organization, inhibiting activation of FAK and Src signaling and decreased MMP9 expression. More importantly, GS treatment decreased mucin MUC4 expression in Capan1 and CD18/HPAF cells through transcriptional regulation by inhibiting Jak/STAT pathway. In conclusion, our results support the utility of GS as a potential therapeutic agent for lethal PC.

1. Introduction

Pancreatic Cancer (PC) is the 10th most commonly diagnosed cancer and 4th leading cause of cancer deaths in the United States with a median 5-year survival of only about 6% [1,2]. PC is often diagnosed at an advanced stage that is highly resistant to conventional chemo-radiation therapy and is difficult to treat [3]. Standard chemotherapy for PC produces only a modest survival benefit in patients with advanced disease and is associated with high toxicity and drug resistance [4]. Hence, effective yet non-toxic therapeutic agents capable of inhibiting the proliferation and metastasis of PC are urgently needed.

Naturally occurring bioactive phytochemicals, due to their non-toxic nature have emerged as promising options for the development of effective alternatives or adjuncts for conventional cytotoxic therapies. Guggulsterone (GS), (4, 17(20)-pregnadiene-3,16-dione), a plant polyphenol derived from the exudates of plant *Commiphora mukkul*, has been used in traditional medicine for treating several ailments including obesity, hyperlipidemia, atherosclerosis, diabetes and osteoarthritis [5]. Recent studies indicate therapeutic and anti-proliferative activity of GS against several human cancers including head and neck, prostate, lung, breast, colon and ovarian cancer, with no apparent signs of toxicity on normal human fibroblast cells, immortalized esophageal cells, non-transformed prostate and colon epithelial cells [6–14]. Besides inhibiting cell proliferation and inducing apoptosis, GS inhibits cell motility and invasion of cancer cells *in vitro* and angiogenesis and metastasis *in vivo* [7,9,12,14]. GS has also been reported to inhibit invasion and metastasis of PC cells through antagonizing Farnesoid X receptor [15]. Further, GS has been shown to increase the efficacy of gemcitabine in gall bladder cancer and PC cells, reverse the multi-drug resistance in breast cancer MCF7 cells [16–18] and enhance radiosensitivity [19].

Abbreviations: PC, pancreatic cancer; MUC4, mucin4; GS, Guggulsterone; STAT, signal transduction and activator of transcription; FXR, Farnesoid X receptor; EMT, epithelial to mechenchymal transition; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; HNSCC, head and neck squamous cell carcinoma; siRNA, small interfering RNA.

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