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14-3-3 zeta is a molecular target in guggulsterone induced apoptosis in Head and Neck cancer cells

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Abstract

Background: The five-year survival rates for head and neck squamous cell carcinoma (HNSCC) patients are less than 50%, and the prognosis has not improved, despite advancements in standard multi-modality therapies. Hence major emphasis is being laid on identification of novel molecular targets and development of multi-targeted therapies. 14-3-3 zeta, a multifunctional phospho-serine/phospho-threonine binding protein, is emerging as an effector of pro-survival signaling by binding to several proteins involved in apoptosis (Bad, FKHRL1 and ASK1) and may serve as an appropriate target for head and neck cancer therapy. Herein, we determined effect of guggulsterone (GS), a farnesoid X receptor antagonist, on 14-3-3 zeta associated molecular pathways for abrogation of apoptosis in head and neck cancer cells.

Methods: Head and neck cancer cells were treated with guggulsterone (GS). Effect of GS-treatment was evaluated using cell viability (MTT) assay and apoptosis was verified by annexin V, DNA fragmentation and M30 CytoDeath antibody assay. Mechanism of GS-induced apoptosis was determined by western blotting and co-IP assays using specific antibodies.

Results: Using in vitro models of head and neck cancer, we showed 14-3-3 zeta as a key player regulating apoptosis in GS treated SCC4 cells. Treatment with GS releases BAD from the inhibitory action of 14-3-3 zeta in proliferating HNSCC cells by activating protein phosphatase 2A (PP2A). These events initiate the intrinsic mitochondrial pathway of apoptosis, as revealed by increased levels of cytochrome c in cytoplasmic extracts of GS-treated SCC4 cells. In addition, GS treatment significantly reduced the expression of anti-apoptotic proteins, Bcl-2, xIAP, Mcl1, survivin, cyclin D1 and c-myc, thus committing cells to apoptosis. These events were followed by activation of caspase 9, caspase 8 and caspase 3 leading to cleavage of its downstream target, poly-ADP-ribose phosphate (PARP).

Conclusion: GS targets 14-3-3 zeta associated cellular pathways for reducing proliferation and inducing apoptosis in head and neck cancer cells, warranting its investigation for use in treatment of head and neck cancer.

Background

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the U.S. and the fourth most prevalent cancer in men worldwide, accounting for over 500,000 new cases annually [1]. The 5-year survival rate is less than 50%, and the prognosis of advanced cases has not improved much over the past three decades [2,3]. Despite standard multi-modality therapeutic interventions, including surgery, radiation and/or chemo-radiotherapy, head and neck cancer patients have a substantial risk of developing second primary tumors, often attributed to "field cancerization" - molecular alterations arising due to chronic carcinogen exposure of the upper aerodigestive tract [4-6]. Moreover, the limited efficacy, lack of safety, and high cost of mono-targeted therapies including EGFR inhibitors, limit their use in head and neck cancer management [7-9]. Hence major emphasis is being laid on identification of novel molecular targets and development of multi-targeted therapies. Clinical development of agents that can delay onset and/or progression could significantly improve the management of head and neck cancer.

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