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Andrographolide inhibits angiogenesis and induces tumor suppressor gene RASSF1A expression in colon cancer cells

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The diterpenoid lactone andrographolide (AGP) isolated from a plant, *Andrographis paniculata*, is known to possess multiple pharmacological activities. It has also been demonstrated to possess anticancer activity in vitro and in vivo. Frequent epigenetic silencing of tumor suppressor genes plays a pivotal role in the development of cancer and several recent reports suggest that suppression of RASSF1A is associated with the advanced grade and stage of many cancers including colon cancer. The goal of the present study was to investigate AGP anticancer activity due to the induction of tumor suppressor genes. T84, Colo 205 and HCT-116 colon cancer cells were treated with AGP IC_{50} and evaluated for expression of tumor suppressor genes by QRT-PCR and immunoblot. Inhibition studies were performed by transfection with gene specific siRNA prior to AGP treatment. AGP induced significantly higher expression of RASSF1A, PTEN, and CDKN2A in colon cancer cells whereas all other tumor suppressor genes tested were either unchanged or suppressed. Similar expression of RASSF1A was also observed in gastric, breast, lung, and prostate cancer cells. Whereas AGP treatment typically down-regulates cyclinD1, transfection of colon cancer cells with RASSF1A specific siRNA resulted in a loss of cyclin D1 suppression. RASSF1A is regulated through the epigenetic methylation of its promoter by DMNT activity which itself is activated by phosphorylated akt. Since Akt is a crucial element of the angiogenesis pathway, we examined the inhibition of this pathway by AGP on T84 and COLO 205 cells. AGP inhibited the transcriptional level of $VEGF_{165}$ in both cell lines as well as vascular epithelial growth factor receptor 1 (VEGFR1) and VEGFR2. Additionally, downstream events including Akt activation and FoxM1 expression were significantly suppressed by AGP. FoxM1 is known to transactivate PTTG1, a major cause of colon cancer cell metastasis. Consistent with FoxM1 suppression, AGP also decreased transcriptional levels of PTTG1. Furthermore, we elucidated the AGP-dependent up regulation of anti-angiogenic molecule TSP-2, is a potent endogenous inhibitor of angiogenesis. These results demonstrate that AGP is a potent inducer of tumor suppressor genes, most notably RASSF1A and that RASSF1A is largely responsible for the cell cycle arrest induced by AGP treatment. These data also demonstrate the anti-angiogenic activity of AGP which may, through suppression of Akt activation, contribute to the up-regulation of RASSF1A.

Biography:

Aditi Banerjee received her Ph.D. from the University of Kalyani, India, in Zoology. She have a track record of driving advanced research by using a natural or synthetic compound to treat for different types of cancer and have extensive experience in cell biology with a focus on developing biomarkers for preclinical and clinical research against gastric ulcer, rheumatoid arthritis, breast cancer. Her early publications directly addressed in the area of basic and translational inflammatory diseases such as rheumatoid arthritis and gastric ulcer. At present, she is interested in the molecular mechanisms underlying the anticancer properties of phytochemicals andrographolide, labdane diterpenoid. Her current research is probing the effect of andrographolide on growth inhibiting, survival and apoptosis signal transduction pathway in colon cancer cells. In 2016, she joined the Department of Pediatrics, Division of Gastroenterology, and University of Maryland School of Medicine as an Assistant Professor.