Gautam Sethi, J Clin Trials 2018, Volume 8
DOI: 10.4172/2167-0870-C1-021

Gautam Sethi

National University of Singapore, Singapore

Modulation of oncogenic transcription factors for cancer therapy

Gamma-tocotrienol, a member of vitamin E superfamily has attracted great attention of late for its anti-proliferative and anti-carcinogenic potential against different cancers. For example, our group has recently reported that anti-proliferative and chemosensitizing effects of γ-tocotrienol are associated with its ability to suppress activation of signal transducers and activator of transcription 3 (STAT3), a pro-inflammatory transcription factor that plays a pivotal role in the survival, proliferation, angiogenesis and chemoresistance of hepatocellular carcinoma. However, the potential of gamma-tocotrienol to overcome chemoresistance in gastric cancer, which is one of the deadliest cancers in Asia-pacific region, has never been explored before. Hence, we investigated the efficacy of gamma-tocotrienol in combination with capecitabine to modulate tumor growth and survival in xenograft mouse model. Gamma-tocotrienol also inhibited expression of various oncogenic proteins, induced PARP cleavage and inhibited NF-κB activation in gastric cancer cells. *In vivo* studies using xenograft model of human gastric cancer demonstrated that gamma-tocotrienol alone suppressed tumor growth and this effect was further potentiated in conjunction with capecitabine. As compared to the vehicle control, gamma-tocotrienol further suppressed the NF-κB activation and expression of cyclin D1, COX-2, ICAM-1, MMP-9 and survivin in tumor tissues obtained from treatment groups. Additionally we noted that gamma tocotrienol can function as a potent inhibitor of angigogenesis in both HUVEC and HCC cells. Overall our results suggest for the first time that gamma-tocotrienol can potentiate the effects of chemotherapy through modulation of multiple biomarkers of proliferation and angiogenesis in diverse cancers.

Biography

Gautam Sethi has completed his Postdoctoral training at University of Texas MD Anderson Cancer Center and then joined Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore in 2008 as an Assistant Professor and promoted to Associate Professor in 2015. The focus of his research over the past few years has been to elucidate the mechanism(s) of activation of oncogenic transcription factors such as NF-kB/STAT3 by carcinogens and inflammatory agents and the identification of novel inhibitors of these proteins for prevention of and therapy for cancer.

phcgs@nus.edu.sg

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