

Thromboxane synthase: A biomarker for targeting therapy of non-small cell lung carcinoma

George G. Chen, Yi Liu, Run-Yue Huang, Ming-Yue Li, Innes Y.P Wan, Calvin SH Ng and Malcolm J. Underwood

The Chinese University of Hong Kong, Hong Kong

Thromboxane synthase (TXS) converts prostaglandin H_2 to thromboxane A_2 (TXA₂). The role of TXS or TXA₂ in tumor growth and metastasis has been documented in a number of cancers. However, their pathways and significance are not fully understood, and furthermore, limited information is available in non-small cell lung carcinoma (NSCLC). Using NSCLC cell lines and mouse lung tumor models, we determined the levels of TXS and TXB2 (a stable metabolite of TXA₂) and explored signal transduction pathway of TXS in NSCLC. It was found that the level of TXB2 was significantly increased in NSCLC, especially those who smoke. Using cigarette smoking carcinogen 4-methylnitrosamino-1-3-pyridyl-1-butanone (NNK), we demonstrated that NNK could stimulate the expression of TXS to produce a significant amount of TXB2. The significance of TXS/TXA₂ in smoking-induced lung cancer was further demonstrated in A/J mice treated with NNK as the level of TXS was significantly higher than the control. Importantly, the inhibition of TXS led to a marked increase in the death of NSCLC cells via inducing apoptosis. The apoptosis induced by the inhibition of TXS was associated with the reduction of nuclear factor kappaB but the enhancement of the nuclear p27. The block of p27 by its siRNA partially but significantly recovered the apoptosis induced by TXS inhibitors. TXS-mediated apoptosis was also found to be related to PI3K/Akt but not JNK and p38 pathways. In summary, NSCLC is associated with the expression of TXS that is at least in part attributable to cigarette smoking. The inhibition of TXS can arrest the growth of NSCLC cells by inducing apoptosis, making TXS a potential therapeutic target.

Biography

George G. Chen had medical training in China and Ph.D. and postdoctoral training in United Kingdom. Currently, he is a Professor at Department of Surgery, Faculty of Medicine, the Chinese University of Hong Kong, and he is also the director of Surgical Laboratories at the same institute. He has published more than 180 papers in peer-reviewed journals and served several journals as a board member.

gchen@cuhk.edu.hk