

Background: Budesonide, an inhaled corticosteroid used in the treatment of asthma, has been shown to be an effective chemopreventive agent in an animal model of adenocarcinoma [Carcinogenesis 1997 Oct 18(10):2015-7]. In humans, although inhaled budesonide for 6 months was not effective in regression of bronchial dysplasia, a significantly higher rate of resolution of CT detected small lung nodules was observed, some of which may represent pre-neoplastic lesions in the peripheral lung [Clinical Cancer Research 2004 Oct 1 10(19): 6502-11]. Despite being used as a drug for treatment of asthma and COPD for over two decades, the in-vivo effects of inhaled steroids on gene expression profiles of bronchial epithelial cells in smokers are still poorly understood.

Objective: The objective of this study is to characterize the effects of inhaled budesonide on the gene expression profiles of bronchial cells from current and former smokers with bronchial dysplasia.

Methods: Bronchial cells were obtained before and after six months of treatment with budesonide 800 mcg BID by inhalation. After two rounds of linear amplification of the extracted RNA, the gene expression profiles were analyzed using the Affymetrix U133A microarray chip.

Results: Using Principal Component Analysis, the effect of active smoking was found to be stronger than the effect of budesonide. In current smokers, more phase 1 genes were up-regulated compared with former smokers. However, phase 2 genes were up-regulated in former smokers but down-regulated in current smokers. Specifically, CYP1B1 was shown to have a two-fold increase in current smokers after Budesonide treatment and approximately a 1.5-fold decrease in former smokers after treatment. In a separate analysis, it was found that genes up-regulated in current smokers had the tendency to be down-regulated in former smokers after treatment. As well, potential genes have been identified which correlate with the response to Budesonide treatment.

Conclusions: A differential effect of Budesonide on gene expression profile was found between current and former smokers at the gene expression level. Furthermore, we have characterized potential genes which correlate with the level of response. Targeting genes, which are differentially regulated by Budesonide between current and former smokers as well as enhancing or curtailing expression of genes correlating with patient response may prove to be beneficial in development of chemopreventive agents. Supported by NIH contract N01-CN85188, & NCI SPORE CA 70907 & NIH 1P01 CA096964