Beta and Alpha Subunits in the Guanylate Cyclase Enzyme in Human Asthma model to Investigate Smooth Muscle Relaxation

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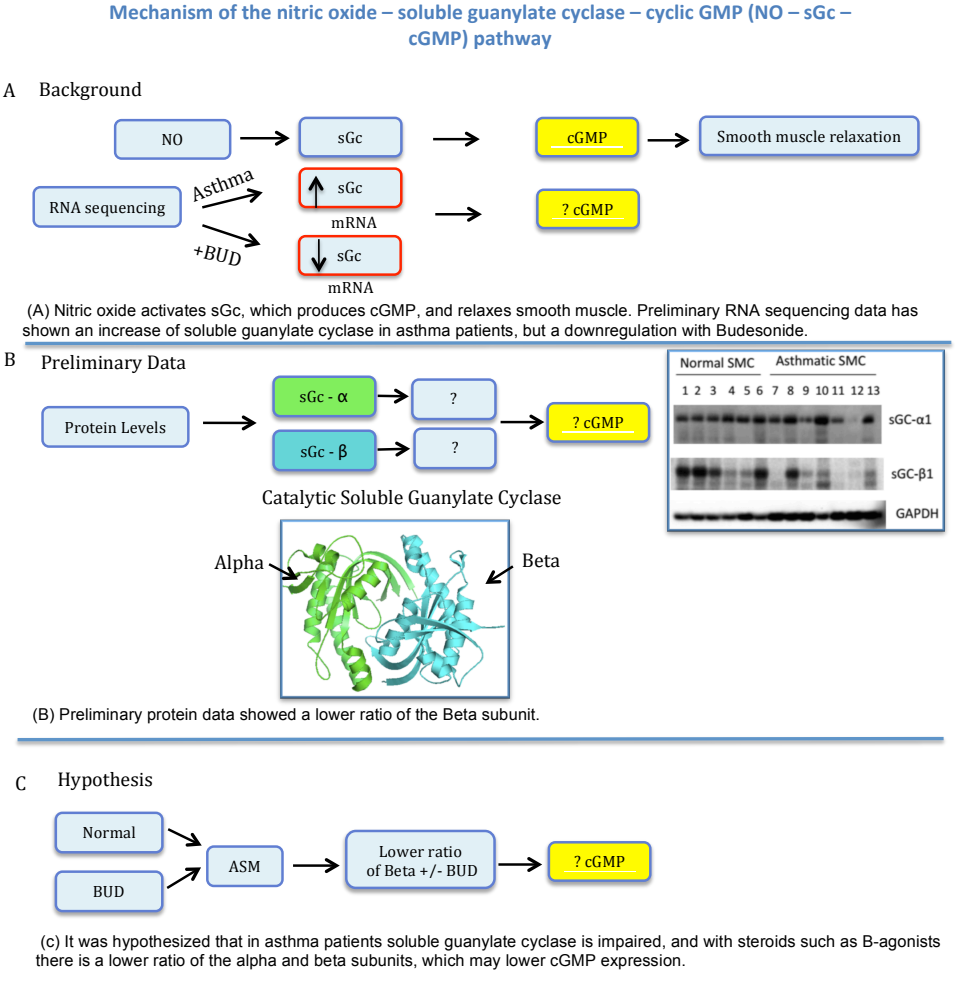
Asthma is characterized by airway hypersensitivity, and common treatments include beta-adrenergic agonist therapy such as budesonide that produce cyclic AMP to relax airway smooth muscle; however, 70% of patients develop resistance to such therapies. In this study, the nitric oxide-soluble guanylate cyclase-cyclic GMP (NO-sGc-cGMP) pathway was investigated as an alternate pharmacologic pathway for asthma therapy and smooth muscle relaxation. Nitric oxide is a smooth muscle relaxing factor that stimulates soluble guanylate cyclase, an airway smooth muscle enzyme, which causes bronchodilation by increasing cGMP (cyclic GMP) levels. Previous studies have found asthma patients are insensitive to NO signaling and used sGc drugs to stimulate the enzyme without the need of NO. The goal of this study was to investigate the NO-sGc-cGMP pathway to determine if there is a differential effect of the soluble guanylate cyclase in asthma patients that prevents relaxation of airway smooth muscle cells by examining sGc subunits.

Preliminary RNA sequencing data has shown an increase of soluble guanylate cyclase in asthma patients, but a downregulation of both subunits with Budesonide. It was hypothesized that in asthma patients soluble guanylate cyclase is impaired, and with steroids such as B-agonists there is a lower ratio of the alpha and beta subunits, which may lower cGMP expression. To examine sGc, the first phase of the study investigated the subunits of the guanylate cyclase enzyme that code for GUCY1A3 and GUCY1B3 genes, respectively. Fatal asthma and non-asthma donor derived airway smooth muscle cells were treated with 24 hours +/- Budesonide. Western blotting was performed to examine the gene expression. A downregulation of the subunit could lead to a lower cGMP expression, which could potentially explain constriction in asthma patients. Further results are pending on the protein level, and future work is needed to measure cGMP levels.



*Guanylate cylase image from http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0057644