The cytoprotective NRF2 Pathway in Cancer Resistance and Lung Disorders.

Chronic Obstructive Pulmonary Disorder (COPD) is characterized by progressive deterioration of the lining of the lung. The major risk factor for COPD is smoking, influenced by additional factors. Recently a genetic analysis indicated that COPD risk was associated with variants in the NFE2L2 gene (commonly called NRF2). The NRF2 gene encodes a DNA-binding transcription factor known for its central role in regulating protective gene expression in response to chemical stress. Other cellular proteins systematically destroy the NRF2 protein, which is present in all cells. When toxic chemicals enter a cell, the NRF2 protein is stabilized and acts to turn on hundreds of genes that deactivate and remove toxins. Dietary studies have linked NRF2 to the protective actions of molecules found in broccoli sprouts and green tea. To better understand the role of NRF2 might be helpful in order to prevent and protect again COPD.

The Wasserman and Sandford laboratories have been independently collaborating with Shyam Biswal (Johns Hopkins University) on NRF2 studies. Our lab has a long-standing goal of understanding how NRF2 recognizes target sequences in DNA. Building bioinformatics methods, the group attempts to predict the cis-regulatory elements in genes that will be functionally bound by the trans-activating NRF2 protein. With Dr. Biswal, the lab has produced the first chromatin immunoprecipitation experiment coupled to massively parallel sequencing. We will reveal the set of protective genes that respond to NRF2 under diverse conditions and across tissues. We will explore the mechanisms by which NRF2 acts by developing accurate models for the prediction of NRF2 binding sites and by coupling the analysis to gene expression data from COPD patients at each GOLD stage of COPD progression to determine those genes, which change in expression.

The firsts results reveal 1256 target sequences bound by NRF2, many of which are present in or adjacent to genes observed to respond to NRF2. The Sandford laboratory has been working with the Biswal group to identify genetic sequence variations in the NRF2 gene that are associated with COPD susceptibility. A promising variant in the regulatory sequences of the NRF2 gene has emerged and is being examined in a secondary cohort of COPD patient samples.

Understanding this network of protection will immediate relevance to ongoing projects across the CIHR, including pharmacogenomics, cancer and respiratory research. Recent advances indicate that NRF2 depends on an as yet unidentified partner protein, which this project will attempt to reveal.

Abstract theme: clinical