ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is characterized by irreversible airflow limitation, abnormal permanent distal air-space enlargement and emphysema in the lungs. Complex interactions between genetic factors and the environment have been suggested predisposition to the disorder. Moreover, the fact that only few individuals out of those exposed to similar conditions develop COPD points to differences in the genetic constitution. Xenobiotic metabolism and oxidative stress are of importance, whose imbalance due to risk factor exposure has the potential to cause COPD and the variations in the genes could be one of the major causative factors. In the present thesis, the polymorphism approach is used to investigate the possible associations of the candidate genes of xenobiotic metabolizing and oxidative stress viz. microsomal Epoxide Hydrolase (mEPHX), Glutathione-S-Transferase P1 (GSTP1), Cytochrome P450 1A1, 1A2 (CYP1A1, CYP1A2) and NADPH oxidase p22phox (CYBA), with COPD. Estimations of plasma malondialdehyde (MDA), reduced glutathione (GSH) levels, Catalase (CAT) and glutathione peroxidase (GPx) activities were measured out to look for a genotype-phenotype correlation. The studies on mice model exposed to acute cigarette smoke revealed the molecular complexity of disease pathogenesis at biochemical and molecular levels. The literature pertinent to the objectives of the present thesis is provided in Chapter 1.

The objectives of the present thesis were the following

The objectives of Chapter 2 was to examine the imbalance in the oxidative status and to ascertain if a relationship existed between oxidative status, BMI and lung function in COPD. Plasma LPO, GSH level, GPx, CAT activities, BMI and FEV1 % predicted were looked for interactions. The study pointed that the COPD patients have impaired status of oxidant-antioxidants balance and the intimate relationship of oxidant-antioxidants with BMI and lung function may potentiates severity of the disease. Even in pathophysiology, the direct correlation between BMI and FEV1 % predicted may be important.
The genetic susceptibility to COPD might depend on variations in detoxification genes that activate and detoxify cigarette smoke products and oxidative stress genes. In this regard Chapter 3 has been divided into two parts to investigate the role of genetic variants of above two pathways. In I\textsuperscript{st} part we attempted to understand the roles of detoxifying gene variants i.e., I105V, A114V of \textit{GSTP1} and Y113H, H139R of \textit{mEPHX} individually or in combination for a possible association with COPD. The estimation of plasma oxidative stress markers such as MDA, GSH, GPx and correlation analysis of the polymorphisms with these biochemical parameters and airflow obstruction was carried out to look for a possible association with the disorder.

The objective of II\textsuperscript{nd} part was to genotype the oxidative stress genes viz. \textit{CYP1A1}, \textit{CYP1A2} and \textit{CYBA} polymorphisms to investigate their association with COPD. The main idea of this study was to ascertain our observations with respect to the above two detoxifying genes in association to COPD. The 462Ile/Val, 3801T/C of \textit{CYP1A1}, −3860G/A of \textit{CYP1A2} and −930A/G, 242C/T of \textit{CYBA} were investigated individually or in combination and their contribution to oxidative stress markers MDA, CAT, GSH and GPx for a possible association with COPD. Correlation of the above polymorphisms with the biochemical parameters was examined for a genotype-phenotype relationship. The findings in continuation to our earlier reports further unraveled the genetic basis of COPD. These findings may find application in predisposition to COPD.

In Chapter 4, we shifted our focus to decipher the involvement of these genetic variants in the susceptibility to High altitude pulmonary edema (HAPE). HAPE is one of the oxidative stress related pulmonary disorder which accounts for most deaths from high altitude (HA) illness. HAPE and COPD, both are pulmonary disorders associated with oxidative stress, suggesting involvement of some common pathways and genes. Complex interactions between genetic factors and the hypoxic environment have suggested predisposition to the disorder. We sought to investigate the involvement of genetic variants of \textit{p22phox} and \textit{GSTP1} in HAPE. The HAPE-p and HAPE-r were compared for the distribution of genotypes, alleles, haplotypes and genotype combinations and correlated with the
biochemical parameter, MDA. The study showed roles of the alleles −930G/242C of \textit{p22phox} and 105V/114V of \textit{GSTP1} their haplotypes and genotypes combinations in association with imbalanced oxidative stress in the susceptibility to HAPE.

In Chapter 5, we looked for the effect of acute-term cigarette smoke (CS) exposure in two vital organs lungs and liver of mice to reveal the molecular complexity of disease pathogenesis. At biochemical level effects of CS were analyzed by estimating activity/levels of detoxifying enzymes, endogenous antioxidants and oxidants. At molecular levels by analyzing RNA, Protein and DNA using various techniques including histopathology, RT-PCR, Western Blotting and Comet assay. The expression of several xenobiotic metabolism and oxidative stress genes were examined at RNA and protein levels, as signal transduction pathways are involved in regulation of different aspects of xenobiotic metabolism, function and oxidative stress. The findings of the study showed differential expression in response to CS.

The details of each investigation in the present thesis are provided after the pertinent Review of Literature.