have demonstrated that blood lymphocyte CYP1A1 could be used a biomarker to predict lung cancer.

P2-023

Promoter analysis of co-expressing genes after exposure to asbestos

Ruosaa, Salla1,4 Nymark, Penny1,2 Hienonen-Kempas, Tuula1 Knuttila, Sakari2,3 Anttila, Sisko1 Hollmén, Jaakko4
1 Health and Work Ability, Biological Mechanisms and Prevention of Work-related Diseases, Finnish Institute of Occupational Health, Helsinki, Finland, 2 Department of Pathology, Haartman Institute and HUSLAB, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland, 3 Helsinki, Finland, 4 Laboratory of Computer and Information Science, Helsinki University of Technology, Espoo, Finland

Background: Occupational exposure to asbestos is associated with the development of asbestosis, malignant mesothelioma, and lung cancer. Research related to the mechanisms by which asbestos fibers cause damage in the cells and which are the mediator genes is important as exact mechanisms underlying asbestos-associated carcinogenesis are not known. Knowledge about the genome-wide alterations involved in asbestos-associated carcinogenesis can be obtained by characterizing changes in gene expression after exposure to the carcinogen or between asbestos-exposed and non-exposed patients using microarrays.

Methods: We have previously analyzed the DNA copy number and gene expression profiles of 14 lung tumors from highly asbestos-exposed and 14 non-exposed patients using microarrays and revealed that a specific aberration profile could be characteristic of lung tumors associated with asbestos-exposure. Furthermore, by exposing human epithelial and mesothelial cells to crocidolite asbestos and performing time-series microarray experiments, we have recently reported asbestos-exposure related temporal changes in gene expression profiles. In this study, the gene expression microarray data from these experiments were combined. Promoter sequence analysis was first applied to clusters of co-expressed genes detected from the cell line data to identify genes that are likely co-regulated by the same mechanisms. Thereafter, common changes between the cell line and patient data were revealed.

Results: 15 transcription factors were identified to be under-represented in the promoter regions of genes with similar temporal expression profiles in comparison to the remaining genes on the array (p<0.00001). Among the under-represented transcription factors were those that have been previously associated with regulation of mitochondria, oxidative stress, and carcinogenesis but not with exposure to asbestos.

Conclusions: The study provides new information about putative transcription factors and mediator genes involved in asbestos-associated carcinogenesis. We show that the integration of gene expression data from cell line and human studies gives insight of the mechanisms underlying asbestos-related carcinogenesis.

P2-024

Association of cytochrome P450 polymorphism and its combination genotypes with lung cancer risk

Shah, Parag P.1,2 Pant, Mohan C.2 Prasad, Rajendra1 Parmar, Devendra4
1 Industrial Toxicology Research Centre, Lucknow, India 2 Dept. of Radiotherapy, KGMU, Lucknow, India 4 Dept.of Pulmonary Medicine, KGMU, Lucknow, India

Background: Globally, lung cancer is the most frequent cancer today and is expected to have a major impact on human health throughout the next decades. The role of tobacco smoking as a major etiologic factor of this malignancy is well established. The gene-environment interaction for cancer development is largely attributed to the action of xenobiotic metabolizing enzymes (XME). Genetic polymorphism is known for the xenobiotic metabolizing cytochrome P450 (CYPs), the phase I enzymes and glutathione-S-transferases (GST), the phase II enzymes, involved in the process of carcinogenesis. As not much information is available on the polymorphism of CYP and GST isoenzymes in Indian population, the present case-control study attempted to investigate the association of polymorphism in CYP1A1, 1B1 and GSTM1 and the combination of these important polymorphisms with squamous cell carcinoma of lung malignancy.

Methods: Patients suffering from squamous cell carcinoma of lung (n=140) and visiting OPD facility of Department of Radiotherapy, King George’s Medical University, Lucknow, India were included in the study. Equal number of age- and sex matched healthy individuals were also enrolled in the study. After obtaining detailed information from each individual, 1.0 ml blood was drawn from them which were processed for isolation of DNA. PCR amplification were carried for studying the polymorphisms in CYP1A1, CYP1B1 and GSTM1 using the standardized protocols.

Results: Our data revealed that the variant alleles of CYP1A1 (both,Msp1, Ile/Val and Bsal) were found to be significantly overrepresented in the lung cancer patients when compared with the controls. Haplotype analysis revealed that haplotype, C-A-C and A-A-T were associated with significant increase in the lung cancer risk. As observed with CYP1A1, the frequency of the variant genotype of CYP1B1 (Arg48Gly/Ala119Ser and Leu432Val) were significantly increased in the patients resulting in significant increase in the lung cancer risk. Haplotypes having 48arginine, 119alanine, 432leucine and 453serine or 48glycine, 119serine, 432valine and 453aspartagine were found to be more prevalent in the cases and were associated with significant increase in the lung cancer risk. Cigarette smoking and tobacco chewing was further found to increase the risk in the cases. The genotype combinations of CYP1A1 and CYP1B1 increased several folds (6-8 folds) the risk associated with lung cancer. Likewise, combination of variant genotypes of CYP1A1 with null genotype of GSTM1 also increased the risk in the cases.

Conclusions: Our case-control study have shown that polymorphism in CYP1A1 and CYP1B1 may modify the risk to lung cancer. Haplotype approach revealed an stronger association of CYP1A1 or 1B1 haplotypes with risk to lung cancer. The increase in risk in cases was further found to be increased in cases carrying combination of variant genotypes of CYP1A1 and 1B1 and GSTM1. Furthermore several fold increase in the risk in smokers and tobacco chewers have demonstrated the importance of gene-environment interactions in the pathogenesis of lung cancer.