DOI 10.18699/SBB-2022-224

Functional enrichment analysis of cytochrome P450 genes differential expression in non-smoking lung cancer patients

Buslaev V.*, Soboleva O.
Institute of Human Ecology of FRC CCC, SB RAS, Kemerovo, Russia
** vladislavbus94@gmail.com*

Key words: lung cancer, non-smokers, cytochromes P-450, GSEA-analysis, NTA-analysis

Motivation and Aim: Lung cancer is featured by high level of morbidity and mortality among the population [1]. It is characterized by presence of two main histopathological forms: small-cell lung cancer and non-small lung cancer. There are many determinants that can modulate individual predisposition to malignant disoders. Smoking is considered as the strongest life style risk factor for lung cancer development. However development of this pathology in non-smoking patients is still under discussion. Cytochromes of P450 family (CYP's) are actively considered as potential biomarkers for oncology development [2]. Normally, these enzymes are able to metabolize products of air pollution in to inactive compounds but also their performance may affect the occurrence of oxidative stress in cells. Active forms of oxygen can directly interact with DNA and initiate mutagenesis. Finally it can lead to uncontrolled cell divisions and cancerogenesis. This study was implemented to test potential contribution of CYP's in to lung cancer development in non-smoking patients.
Methods and Algorithms: The most frequently studied genes from this group (*CYP2E1*, *CYP2A6*, *CYP4Z2P*, *CYP19A1*, *CYP4A22*, *CYP4B1*) were chosen for present analytic survey. Transcriptome dataset of non-smoking women with lung cancer obtained from NCBI GEO database was used for investigation of these genes contribution. Gene set enrichment analysis (GSEA) method was used to estimate level of cytochrome P450 genes association with lung cancer. Network topology analysis (NTA) and TCGA database were applied to reveal protein-protein interactions of cytochromes during cancerogenesis. This method along with Gene Ontology database application allowed to detect crucial biological processes (top enriched GO categories) in those these cytochromes are involved.
Results: As a result GSEA functional enrichment analysis showed significant association between cytochromes P450 enhanced expression and lung cancer development in non-smoking female patients. Along with GSEA-plot significant parameters of p-value and normalized enrichment score (NES) were registered (Fig. 1). Crucial enzymes that were involved in detoxification metabolic processes demonstrated significant interactions with CYP4B1 protein (Fig. 2). Among top 10 enriched GO categories signaling pathways associated with metabolism of benzene-containing compounds (GO:0042537) and drug catabolic process (GO:004737) were detected (Fig. 3).
Conclusion: CYP genes that were tested via GSEA-analysis can be considered as potential biomarkers for lung cancer formation in non-smokers. They can act in gene networks and exhibit their features. Biological signaling pathways that can make potential contribution in this pathology were determined by NTA analysis. In this case lung cancer is possibly arises due to specificity of xenobiotics metabolism.

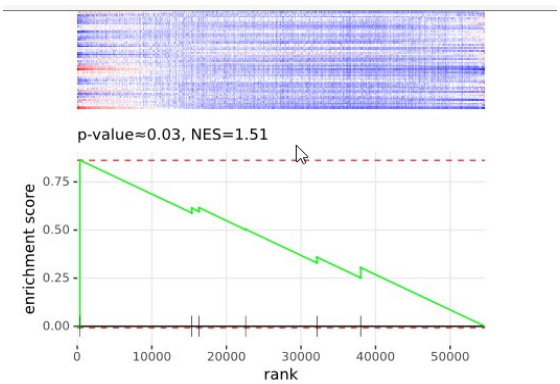

Fig. 1. GSEA functional enrichment analysis of CYP-genes

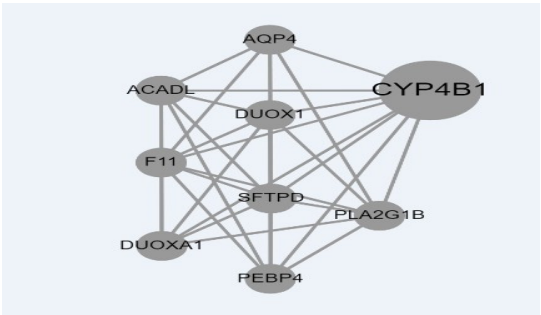

Fig. 2. Protein-protein interactions of CYP4B1

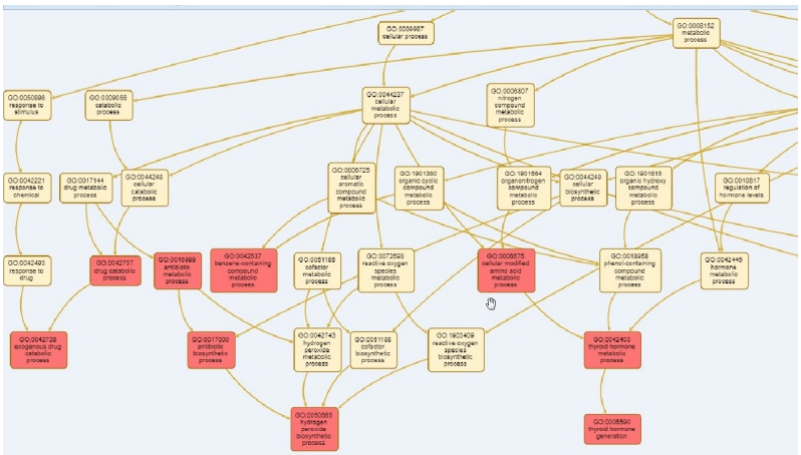

Fig. 3. Top enriched GO-categories (marked by red) associated with CYP's and lung cancer

Acknowledgements: The study is supported by state assignment (Project No. 0286-2022-0008).

References

1. Bray F. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
2. Mittal B. et al. Cytochrome P450 in cancer susceptibility and treatment. *Adv Clin Chem.* 2015;71:77-139.