AMITRIPTYLINE; A SYSTEMS BIOMEDICINE-ORIENTED REPOSITIONED DRUG CANDIDATE FOR BREAST CANCER

*Fadime Dilşad Taş[1], Keziban Okutan[2], Tuğba Ceylan[1], Ömer Faruk Özkaya[2] and Büşra Aydın[1]**

[1]Department of Bioengineering, Faculty of Engineering and Architecture, Konya Food and Agriculture University, Konya, Turkey
[2]Department of Molecular Biology and Genetics, Faculty of Agriculture and Natural Sciences, Konya Food and Agriculture University, Konya, Turkey. phone: +90 507 442 86 42, email: busra.aydin@gidatarim.edu.tr *Corresponding author

Introduction: Breast cancer (BRCA) is a disease where the growth of breast cells is out of control. According to WHO's latest cancer statistics, the BRCA is the world's most prevalent cancer. In clinic, there are possible treatments that target cancer cells such as chemotherapy, radiation, or hormone therapies. However, these treatments have long-term side effects that can occur even multiple years after the treatment which may lead to even notorious consequences. **Methods:** Transcriptome-level BRCA gene expression profiling dataset with accession number GSE42568 was retrieved from GEO database and analyzed via GEO2R. Overall design of the dataset was consisting of 104 breast cancer biopsies and 17 healthy breast biopsies. As a result of gene expression analysis, differentially expressed genes (DEGs) were elucidated through p-value and FC cut-offs, which are 0.05 and 2, respectively. Consequently, the elucidation revealed 1540 DEGs in total which 788 of them upregulated and 752 of them down regulated. DEGs were functionally enriched via ConsensusPathDB. Biological network constructions around all DEGs were performed via protein-protein (BioGrid), miRNA gene (mirTarbase), and transcriptional factor gene interactions (TRRUST). These interaction networks were visualized via Cytoscape software and topological-network-analysis was performed using degree and betweenness-centrality metrics. Hubs of interaction networks were revealed and used further for survival and clustering analyses. The consequential results achieved through survival and clustering analyses were used to obtain repositioned drug candidates for BRCA via L1000CDS^2 search engine. **Results:** As a result of functional-enrichment-analysis, antigen-processing and presentation, focal and cell adhesion pathways were significantly enriched. 50 drug candidates identified through drug repositioning based on transcriptional factor interaction, protein-protein interactions, and miRNA-level data combinations. Besides reporter signatures revealed from networks were utilized for determining relations of drugs to reverse observed changes in gene expression regarding BRCA. Potential of these drugs on BRCA was reviewed comprehensively through literature. The drug candidates were ranked according to 1-cos(α) search score. One of repositioned candidate drugs having highest score, amitriptyline, is used in clinic for treatment of migraine and depression. **Discussion:** We presented transcriptomic landscape of breast cancer through three-layered biological network including transcription factor-gene, protein-protein, and miRNA-gene interactions data combinations. Amitriptyline is proposed as repositioned drug, which will be further analyzed using BRCA cell lines, for management of BRCA based on transcriptome-based multi-level biological-network-interactions.

Keywords: Breast cancer, amitriptyline, drug repositioning, network analysis, differentially expressed genes, transcriptome, gene expression