Notification No. F.NO. COE/ Ph.D./(Notification)/532/2023

Date of Award 14/04/2023

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Topic of Research: Statistical Analysis of RNA-seq Data for Disease Signature Identification and Drug Discovery

FINDINGS

Integrating the computational and statistical approaches in drug designing and development process decreases the time consumption to several folds. This research deals with implementing differential gene expression (DGE) profiling for better reasoning of Zika virus (ZIKV) and Coronavirus infection over human cell lines. We applied inferential statistics based bioinformatical approach for biomarker (DEGs) identification via DGE analysis, co-expression network analysis for hub gene detection, and enriched pathways analysis detecting key dysregulated human pathways upon ZIKV and Coronavirus infection. We also performed docking studies of herbal drugs evidenced in treating other respiratory ailments; and the proteins encoded by identified DEGs for lead discovery as possible treatment of coronavirus infection.

The first part of the research deals with ZIKV infection profiling, that successfully identified the promising DEGs of human neuronal cell infection. DDIT3, CEBPB, TRIB3, XBP1, KLF15, JDP2, BHLHE41, CREB3L1, RELB, TTF2, E2F2 were transcription factors; XBP1, PPFIA4 were hub genes with maximum associations making them potential antiviral drug targets. Most of them were upregulated. The key findings from enrichment analysis of DEGs in ZIKV infection suggested their potential association to COPD and a reduction in HDL-C, both of which increase the risk of heart disease. After literature mining, discovered PPFIA4 gene is associated with Atrial fibrillation, linked to acute ZIKV infection positivity. Additionally, DEGs might be associated to Type-2 diabetes as pathway analysis revealed dysregulated insulin resistance pathway in ZIKV infection. Literatures suggests insulin resistance in patients with obesity, type 2 diabetes, cardiovascular diseases, etc. Type 2 diabetics has dysregulated insulin resistance pathway with reduced IRE-1 receptor signaling

and some research suggests blocking IRE1 pathway can reverse ZIKV-induced dysregulation of spermatogenesis and neurogenesis too. Hence, DEGs in ZIKV infection might contribute alteration in insulin resistance pathway leading to Type-2 diabetes via suspected role of IRE1 are needed.

The other part of research deals with Coronavirus infection profiling where SRSF6, HECTD1, CBX3, and DDX17 were identified as hub genes. Research suggested that irrespective of coronavirus strain type i.e. SARS-CoV and SARS-CoV-2, majority of same DEGs were identified. It was observed that the higher coronavirus infection exposure led to higher gene expression rates suggesting initial infection has least functional disturbance, while increase time of exposure deteriorates functional systems and pathways. TNF, cytokine, NF-kB, TLR, TCR, and BCR signaling pathways related to immune are found to be dysregulated. Thus, Coronavirus infection directly damage immune system and those cellular systems which are known to balance and counter external infection.

The next part dealt with discovery of potential lead compounds targeting the identified DEGs in Coronavirus infection. The three natural medications namely apigenin, quercetin, and resveratrol might be viable therapeutic candidates against COVID-19 infection as well, since they have been demonstrated as a cure for other respiratory ailments upon performing literature survey. Hence the efficacy for the identified DEGs (SRSF6, DDX17, CBX3, and HECTD1) in coronavirus profiling was investigated. We observed that the three drugs bind almost in the same binding region of the proteins. Among the three drugs, Quercetin has the best binding affinity with HECTD1 protein. All three drugs were found to provide better binding affinities for DDX17, HECTD1. Here, it could be concluded that these three herbal drugs display better binding possibilities in terms of ΔG (Gibb's free energy).

This research study provides in-silico approach for differential gene expression analysis for viral infections in human to be identified as possible biomarkers, and the docking studies with herbals drugs and could be extended to in-vitro and in-vivo study in terms of future perspective and the same is the limitations of this study.