International Journal of Biotechnology and Biomedical Sciences
p-ISSN 2454-4582, e-ISSN 2454-7808, Volume 5, Issue 1; January-June, 2019 pp. 78-78

http://www.krishisanskriti.org

Identification of miRNA-TF-gene Motifs as Candidate Temporal Markers during Hypoxic Stress

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Abstract

Introduction: *Hypoxia is a complex pathophysiological condition which arises when the body tissue is deprived of adequate oxygen supply due to various pathological or environmental conditions. Identification of temporal markers during hypoxic-stress is important to predict hypoxia-adaptation with time. In the present study, network biology approaches have been used to identify overrepresented modules in the tripartite miRNA-TF-gene coregulatory network and propose them as potential temporal markers. Thestudy provides a proof-of-concept and could be applied on gene-sets related to other complex hypoxia-associated disorders to identify potential biomarker candidates for diagnostic, prognostic and therapeutic purposes.*

Methodology and Results*: Feed-Forward Loops(FFLs) arethree-node subgraph comprising of a Transcription Factor (TF), a miRNA and either of themregulating each other or both together regulating a target gene.FFLs have been identified as potential markers in a number of multifactorial disorders like myocardial infarct, schizophrenia, cancer, etc. To begin, genes which differentially express with the change in duration of hypoxic-exposure were collected from HypoxiaDB database. Differentially expressed genes on 8 hrs, 16 hrs and 24 hrs of 1% hypoxia exposure were collected. Overrepresented miRNAs for these three temporal gene-sets were identified using hypergeometric distribution function followed by the Benjamini–Hochberg (BH) adjustment with a cut-off value of 0.05. Further, miRNA-TF, miRNA-gene, TF-gene, TF-miR interaction was added to construct three miRNA-TF-gene coregulatory networks corresponding to three temporal hypoxia-exposures (8hrs, 16 hrs and 24 hrs). FFLs in each network were identified using "igraph" R package and their significance were calculated using randomization process by "motif discovery" plugin of Cytoscape 3.6.1.10; 58 and 875 FFLs were identified in 8 hrs, 16 hrs, 24 hrs co-regulatory network respectively. The ten FFLs obtained in 8 hrs of hypoxia exposure were unique and were not present in longer exposure times. Their pathway enrichment analysis identified "interleukinsignalling" as the most enriched term. Interleukinsignalling machinery is known to control responses such as inflammation, immune response, cell growthetc. These pathways are hallmarkresponses during the early stages of hypoxic- exposure. Nine FFLs were common between 16 hrs and 24 hrs hypoxic stress networks. Their pathway enrichment identified "TP53 gene expression" as the most enriched pathway followed by "interleukins signalling". TP53 controls the cell cycle mechanisms, which further regulates cell fate towards cell-proliferation/cell-differentiation/apoptosis, etc. Our study have revealed that interleukin signaling and TP53 influence the cellular machinery during the early onslaught of hypoxic-stress until 24 hrs. Beyond this time, HIF-1 (master regulator of many hypoxia-responsive genes) expresses and activates various pathways for hypoxic-adaptation. The temporal FFLs could thus be potential markers to study time-dependent hypoxia-responses. Therefore two miRNAs (hsa-mir-20a, hsa-mir-17), four TFs (STAT5B, JUN, SMAD3, CCND1) and the gene (APP) belonging to ten FFL motifs are proposed as biomarker candidates for 0 to 8 hrs of hypoxia-exposure. Similarly, onemiRNA (hsa-mir-16-5p), three TFs(JUN, ATF3, TP53) and the gene (VEGFA) belonging to nine FFL motifs are proposed as biomarker candidate for 8 to 24 hrs hypoxic exposure.*