

# IDENTIFICATION OF REGULATORY CIRCUITS THROUGH NETWORK ANALYSIS: HSA-MIR-200B AND CFL2 AS IMPORTANT COMPONENT IN INTESTINAL GASTRIC CANCER PATHOGENESIS

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**INTRODUCTION AND OBJECTIVES:** Intestinal gastric cancer (IGC) carcinogenesis results from complex interplay between environmental and molecular factors, ultimately contributing to disease development. Integrating data from high-throughput analyses from expression of mRNAs and microRNAs have been performed in many cancers. However, there are no integration analysis that including proteomic data in IGC. Therefore, in this study we used integrative bioinformatic analysis to investigate IGC high-throughput molecular data and uncover interactions among differentially expressed genes, microRNAs and proteins and their roles in IGC. **MATERIAL AND METHODS:** RNA-seq and clinical data of tumor (T) tissues (n = 180) and adjacent nontumor (NT) tissues (n = 18) from IGC were obtained from The Cancer Genome Atlas. Differentially expressed genes (DEGs), microRNAs (DEMs) and proteins (DEPs) between T and NT were identified. Integrated regulatory networks were built based on DEGs overlapping DEPs and validated interactions between DEMs-DEGs. Networks were visualized using Cytoscape; functional enrichment analysis was performed and IGC hubs were determined; the relationship between hubs and patient clinicopathological characteristics as well as the correlation between expression levels of selected DEG-DEM hub pairs were tested; receiver operating characteristic and survival analysis of DEMs and DEGs hubs were also performed. **RESULTS AND CONCLUSION:** An integrated network was generated based on experimentally validated microRNA-gene/protein interaction data, with 3 regulatory circuits involved in a complex network contributing to IGC progression. Key regulators were determined, including 23 microRNAs and 15 gene/protein hubs. The regulatory circuit networks are associated with hallmarks of cancer, e.g., cell death, apoptosis and the cell cycle, immune system and epithelial to mesenchymal transition, indicating that different mechanisms of gene regulation impact similar biological functions. Altered expression of hubs was related to the clinicopathological characteristics of IGC patients and showed good performance in discriminating tumors from adjacent nontumor tissues and in relation to T stage and overall survival (OS). Interestingly, expression of upregulated hub hsa-mir-200b and its downregulated target hub gene/protein CFL2 are related not only to pathological T staging and OS but also to changes during IGC carcinogenesis. Our study suggests that regulation of CFL2 by hsa-miR-200b is a dynamic process during tumor progression and that this control plays essential roles in IGC development. Overall, the results indicate that this regulatory interaction is an important component in IGC pathogenesis. Also, we identified novel molecular interplay between microRNAs, proteins and genes associated with IGC in a complex biological network and hubs closely related to IGC carcinogenesis as potential biomarkers.

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