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Identification of Hub Genes in the Development of Atherosclerosis

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Abstract : Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids, immune cells, and extracellular matrix in the arterial walls. This pathological process can lead to the formation of plaques that can obstruct blood flow and trigger various cardiovascular diseases such as heart attack and stroke. The underlying molecular mechanisms still remain unclear, although many studies revealed the dysfunction of endothelial cells, recruitment and activation of monocytes and macrophages, and the production of pro-inflammatory cytokines and chemokines in atherosclerosis. This study aimed to identify hub genes involved in the progression of atherosclerosis and to analyze their biological function in silico, thereby enhancing our understanding of the disease's molecular mechanisms. Through the analysis of microarray data, we examined the gene expression in media and neo-intima from plaques, as well as distant macroscopically intact tissue, across a cohort of 32 hypertensive patients. Initially, 112 differentially expressed genes (DEGs) were identified. Subsequent immune infiltration analysis indicated a predominant presence of 27 immune cell types in the atherosclerosis group, particularly noting an increase in monocytes and macrophages. In the Weighted gene co-expression network analysis (WGCNA), 10 modules with a minimum of 30 genes were defined as key modules, with blue, dark, Oliver green and sky-blue modules being the most significant. These modules corresponded respectively to monocyte, activated B cell, and activated CD4 T cell gene patterns, revealing a strong morphological-genetic correlation. From these three gene patterns (modules morphology), a total of 2509 key genes (Gene Significance >0.2, module membership>0.8) were extracted. Six hub genes (CD36, DPP4, HMOX1, PLA2G7, PLN2, and ACADL) were then identified by intersecting 2509 key genes, 102 DEGs with lipid-related genes from the Genecard database. The bio-functional analysis of six hub genes was estimated by a robust classifier with an area under the curve (AUC) of 0.873 in the ROC plot, indicating excellent efficacy in differentiating between the disease and control group. Moreover, PCA visualization demonstrated clear separation between the groups based on these six hub genes, suggesting their potential utility as classification features in predictive models. Protein-protein interaction (PPI) analysis highlighted DPP4 as the most interconnected gene. Within the constructed key gene-drug network, 462 drugs were predicted, with ursodeoxycholic acid (UDCA) being identified as a potential therapeutic agent for modulating DPP4 expression. In summary, our study identified critical hub genes implicated in the progression of atherosclerosis through comprehensive bioinformatic analyses. These findings not only advance our understanding of the disease but also pave the way for applying similar analytical frameworks and predictive models to other diseases, thereby broadening the potential for clinical applications and therapeutic discoveries.

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