

Graphical Modeling of Gene Expression in Monocytes Suggests Molecular Mechanisms Explaining Increased Atherosclerosis in Smokers

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Smoking is a risk factor for atherosclerosis with reported widespread effects on gene expression in circulating blood cells. We hypothesized that a molecular signature mediating the relation between smoking and atherosclerosis may be found in the transcriptome of circulating monocytes.

Genome-wide expression profiles and counts of atherosclerotic plaques in carotid arteries were collected in 248 smokers and 688 non-smokers from the general population. Patterns of co-expressed genes were identified by Independent Component Analysis (ICA) and network structure of the pattern-specific gene modules was inferred by the PC-algorithm. A likelihood-based causality test was implemented to select patterns that fit models containing a path "smoking?gene expression?plaques". Robustness of the causal inference was assessed by bootstrapping. At a FDR ≤ 0.10 , 3,368 genes were associated to smoking or plaques, of which 93% were associated to smoking only. SASH1 showed the strongest association to smoki