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Scientists discover gene module underlying atherosclerosis development

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By measuring the total gene activity in organs relevant for coronary artery disease (CAD), scientists at the Swedish medical university Karolinska Institutet have identified a module of genes that is important for the recruitment of white blood cells into the atherosclerotic plaque. The findings, which are to be published in the open-access journal *PLoS Genetics*, suggest that targeting the migration of white blood cells in the development of atherosclerosis may help to reduce the risk for adverse clinical effects such as ischemia and myocardial infarction.

Atherosclerosis is the major cause of myocardial infarction and stroke, and is responsible for half of all deaths in Sweden and other Western countries. Complications of atherosclerosis are rapidly increasing as a major cause of death also in developing countries; the World Health Organisation has predicted that this will become the number one killer by 2010.

"It has been an exciting research project, which has gone on for nearly seven years, involving many different disciplines from thoracic surgeons to mathematicians", says team leader Dr. Johan Björkegren at Karolinska Institutet in Stockholm. "I believe that this kind of clinical study will follow in the aftermath of the large number of ongoing genome-wide association studies."

Rather than individual genes or individual DNA variants, the discovery encompasses a group of 128 functionally related genes in a 'module' or 'network', which explains their mutual interactions. The involvement of

most of these genes in CAD has not previously been known, but it has been known that they are involved in endothelial function and angiogenesis.

Through the collaboration with Dr. Eric Schadt's team at Washington University, Seattle, the researchers were also able to take advantage of previously published genome-wide association studies (GWAS) of CAD to show that the gene module they have discovered is enriched for inherited risk of developing myocardial infarction.

"The GWAS are genetic epidemiology studies often involving tens of thousands of patients and controls, originally designed to link isolated DNA locus to the risk of developing complex common disorders, such as atherosclerosis", says Dr Björkegren. "These studies now need to be complemented with clinical studies where the patients also are screened for intermediate molecular phenotypes in disease-relevant organs. The computational capacities and expertise required to address simultaneously all molecular activities and their relative risk-enrichment are available, all that remains is to start recruiting this kind of cohorts."

The findings suggest that the severity of atherosclerosis depends on the rate of the migration of white blood cells from the blood into the atherosclerotic plaques. Although this pathway is already known to play a role in atherosclerosis, the Swedish findings suggest that it is the rate limiting step for disease progression. However, Dr Björkegren admits that the exact roles of all 128 genes in atherogenesis remain unexplained. Future studies will focus on understanding the details of how these genes actually contribute to atherosclerosis in cell cultures and animal model systems.

More information: 'Multi-Organ Expression Profiling Uncovers a Gene Module in Coronary Artery Disease Involving Transendothelial Migration of Leukocytes and LIM Domain Binding 2; The Stockholm

Atherosclerosis Gene Expression (STAGE) Study', Sara Hägg, Josefin Skogsberg, Jesper Lundström, Peri Noori, Roland Nilsson, Hua Zhong, Shohreh Maleki, Ming-Mei Shang, Björn Brinne, Maria Bradshaw, Vladimir B. Bajic, Ann Samnegl′rd, Angela Silveira, Lee M. Kaplan, Bruna Gigante, Karin Leander, Ulf de Faire, Stefan Rosfors, Ulf Lockowandt, Jan Liska, Peter Konrad, Rabbe Takolander, Anders Franco-Cereceda, Eric E. Schadt, Torbjörn Ivert, Anders Hamsten, Jesper Tegnér, and Johan Björkegren. PLoS Genetics, online publication, 3 December 2009, doi: 10.1371/journal.pgen.1000754

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