atherosclerosis

Atherosclerosis newsletter

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This issue of *Atherosclerosis* contains several interesting reports on novel potentially important players in the pathogenesis of atherosclerotic cardiovascular diseases.

A comprehensive contribution of genetic variations of the insulin-like growth factor 1 signalling pathway to stroke susceptibility

Stroke is a major public health concern, leading to tremendous health and economic burden globally. The pathogenesis of stroke is highly complex, and both genetic and environmental factors could increase predisposition. Arterial endothelial dysfunction and atherosclerosis are important risk factors for stroke. The insulin-like growth factor (IGF)-1 signalling pathway has been implicated in the pathogenesis of atherosclerosis; however, the mechanism underlying its role in stroke remains unexplained. Yao et al. aimed to explore the effects of genetic polymorphisms in the IGF1 pathway on stroke in the Chinese Han population.

Twenty-six single-nucleotide polymorphisms (SNPs) in IGF1 pathway genes were genotyped in a case-control study consisting of 2070 stroke cases and 2243 controls. Main genetic effects and gene-gene interactive effects of the IGF1 pathway were evaluated. Weighted genetic risk scores (wGRS) were computed, and the associations between wGRS and gene expression analysed.

The variants at growth hormone-releasing hormone (*GHRH*) rs6032470 were significantly associated with high risk of hemorrhagic stroke (HS). Significant additive interaction between rs6032470 and gender was detected for HS and ischemic stroke (IS). The association of rs6032470 and stroke was stronger in males. Moreover, a significant gene-gene interaction of rs6032470-rs1874479 IGF binding protein 1 (*IGFBP1*) in relation to HS risk was identified. *IGF1* mRNA expression was significantly upregulated in IS, while it was linearly downregulated across rs6214 genotypes. In addition, *IGFBP3* transcript variant 2 mRNA level was negatively correlated with wGRS.

These results indicate that the IGF1 signalling pathway genes potentiate the risk of stroke through main effects and gene-gene interactions. The genetic effect of *GHRH* rs6032470 on stroke is gender dependent. wGRS of IGF1 pathway genes may be an independent predictor of stroke risk.

Progression of coronary calcium burden and carotid stiffness in patients with essential thrombocythemia associated with *JAK2* V617F mutation

Myeloproliferative disorders are a heterogeneous group of malignancies that arise from a transformation of hematopoietic stem cells. The main myeloproliferative neoplasms are essential thrombocythemia (ET), polycythemia vera, and primary myelofibrosis. Patients with these neoplasms often succumb to cardiovascular events, but little is known on the early stages of their vascular disease. Anžič Drofenik et al. studied how patients with ET, without overt atherosclerotic disease, carrying the mutation in the Janus kinase 2, (JAK2) V617F (present in a high number of subjects with myeloproliferative disorders) differed from control subjects in the progression of carotid artery stiffness and preclinical atherosclerosis.

Thirty-six patients with JAK2 V617F positive ET and 38 age-, gender- and Framingham coronary heart disease (CHD) risk score-matched control subjects were examined twice within 4 years. Clinical and laboratory testing, echo-tracking ultrasound of carotid arteries, coronary calcium measurement and digital plethysmography were performed.

Coronary calcium correlated with the Framingham CHD risk score at the first examination in the control group but not among the ET patients. Both groups had coronary calcium progression, but the outliers were more prominent among ET patients. Carotid artery stiffness increased with time more in the ET patients than in the control group. There was no correlation between carotid stiffness and Framingham CHD risk in either group. Digital endothelial function did not change.

The results showed that carotid artery stiffness progressed significantly faster in ET patients than in control subjects during the 4 years of follow-up. Coronary calcium correlated with the Framingham CHD risk only in control subjects. These results suggest that JAK2 V167F mutation promotes stiffening of the carotid arteries and acts as a non-classical risk factor for atherosclerosis.

Legumain is upregulated in acute cardiovascular events and associated with improved outcome - potentially related to anti-inflammatory effects on macrophages

Proteases secreted by macrophages play important roles in plaque progression and destabilization in atherosclerosis by degrading the extracellular matrix (ECM) in the fibrous cap. Matrix metalloproteases (MMPs) are well known markers of cardiovascular disease (CVD) progression. However, the roles of other proteases, like members of the cysteine protease family, are less studied.

Lunde at al. previously found increased levels of the cysteine protease legumain in plasma and plaques from patients with carotid atherosclerosis. In this study, they further investigate legumain during acute cardiovascular events.

Circulating levels of legumain from patients of the SUrrogate markers for Micro- and Macrovascular hard endpoints for Innovative diabetes Tools (SUMMIT) Malmö cohort and legumain released from platelets were assessed by enzyme-linked-immunosorbent assay. Quantitative PCR and immunoblotting were used to study expression, while localization was visualized by immunohistochemistry.

The levels of circulating legumain were associated with the presence of CVD in non-diabetics, with no relation to outcome. In symptomatic carotid plaques and in samples from both coronary and intracerebral thrombi obtained during acute cardiovascular events, legumain co-localized with macrophages in the same regions as platelets. *In vitro*, legumain was shown to be present in and released from platelets upon activation. In addition, THP-1 macrophages exposed to releasate from activated platelets showed increased legumain expression. Interestingly, primary peripheral blood mononuclear cells stimulated with recombinant legumain promoted anti-inflammatory responses. Finally, patients from the Post conditioning in ST-Elevation Myocardial Infarction (POSTEMI) cohort had significantly higher circulating legumain before and immediately after percutaneous coronary intervention compared with healthy controls, and high levels were associated with improved outcome.

These data demonstrate that legumain is upregulated during acute cardiovascular events and is associated with improved outcome.

In their editorial, de Jager and Hoefer further comment on the role of legumain in the biological pathways involved in atherosclerosis and the presumed origin of its increased levels in the circulation.

Effect of a coronary-heart-disease-associated variant of ADAMTS7 on endothelial cell angiogenesis

Genome-wide association studies (GWAS) have shown the association between genetic variation at the *ADAMTS7* (a disintegrin and metalloprotease with thrombospondin motif 7) locus and susceptibility to coronary artery disease (CAD). Furthermore, clinical studies have shown that the CAD-associated variants at this locus are also associated with worse clinical outcome. Pu et al. previously identified a Ser214-to-Pro substitution in *ADAMTS7* resulting in lowered proteolytic activity, reduced thrombospondin-5 (TSP-5) cleavage by ADAMTS7, and decreased vascular smooth muscle cell migration. In this study, the authors investigated whether this substitution affects angiogenesis, since neovascularization plays an important role in atherosclerosis.

ADAMTS7 knockdown in vascular endothelial cells (ECs) attenuated their angiogenesis potential, while increased ADAMTS7-Ser214 expression had the opposite effect, leading to increased ECs migratory and tube formation ability. Proteomics analysis or culture media conditioned by ECs revealed that thrombospondin-1 is increased by ADAMTS7 knockdown but decreased by ADAMTS7-Ser214 overexpression. A cleavage assay indicated that ADAMTS7 has thrombospondin-1 degrading activity, which is reduced by the Ser214-to-Pro substitution. The pro-angiogenic effect of ADAMTS7-Ser214 diminished in the presence of a thrombospondin-1 blocking antibody.

The ADAMTS7 Ser214-to-Pro substitution affects thrombospondin-1 degradation, thereby promoting atherogenesis through increased EC migration and tube formation.