Atherosclerotic Abdominal Aortic Aneurysm and the Interaction Between Autologous Human Plaque-Derived Vascular Smooth Muscle Cells, Type 1 NKT, and Helper T Cells

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Abstract
Immune cell infiltration, vascular smooth muscle cell (VSMC) proliferation, and apoptosis are pathological hallmarks of atherosclerosis. The multifocal, chronic, and inflammatory nature of this disease of the cardiovascular system complicates targeted cellular therapy and emphasizes the need to understand the role and interaction of immune cells with VSMCs. We characterized the immune cell subsets present in human atherosclerotic tissue derived from atherosclerotic abdominal aortic aneurysm (AAA) and expanded them to study their interaction with autologous plaque-derived VSMCs in vitro. We show here that apart from T lymphocytes, plaque infiltrates consist of lots of NK cells and significat proportions of NKT cells that express T cell receptor (TCR) αβ, CD4, and the NK markers CD56 and CD161. The infiltrates are predominantly IFN-y-producing Type 1 lymphoid cells. When cocultured, the T and NKT cells adhere to VSMCs. CD4$^+$ T cells enhance VSMC proliferation. VSMCs in turn enhance CD4$^+$ CD161$^+$ NKT but not CD4$^+$ or CD8$^+$ T cell proliferation. CD4$^+$ CD161$^+$ NKT cells inhibit VSMC proliferation by inducing apoptosis.Our results suggest that the interactions of Type 1 CD4$^+$ T and CD4$^+$ CD161$^+$ NKT cells with VSMCs may regulateVSMC proliferation and death respectively in atherosclerosis and the balance of these interactions could determine plaque stability. (**Circ Res. 2005;96:675-683.**)

Key Words: atherosclerotic abdominal aortic aneurysm; helper T cells; NKT; vascular smooth muscle cells; atherosclerosis

Common Variants in Myocardial Ion Channel Genes Modify the QT Interval in the General Population. Results From the KORA Study

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Abstract
Altered myocardial repolarization is one of the important substrates of ventricular tachycardia and fibrillation.The influence of rare gene variants on repolarization is evident in familial long QT syndrome. To investigate the influence of common gene variants on the QT interval we performed a linkage disequilibrium based SNP association study of four candidate genes. Using a two-step design we analyzed 174 SNPs from the KCNQ1, KCNH2, KCNE1, andKCNE2 genes in 689 individuais from the population-based KORA study and 14 SNPs with results suggestive of association in a confirmatory sample of 3277 individuais from the same survey. We detected association to a gene variant in intron 1 of the KCNQI gene (rs757092, +1.7 ms/allele, P=0.0002) and observed weaker association to avariant upstream of the KCNE1 gene (rs727957, +1.2 ms/allele, P=0.0051). In addition we detected association to twoSNPs in the KCNH2 gene, the previously described K897T variant (rs1805123, -1.9 ms/allele, P=0.0006) and a gene variant that tags a different haplotype in the same block (rs3815459, +1.7 ms/allele, P=0.0004). The analysis of additive effects by an allelic score explained a 10.5 ms difference in corrected QT interval length between extreme score groups and 0.951 of trait variance (P<0.00005). These results confirm previous heritability studies indicating that repolarization is a complex trait with a significant heritable component and demonstrate that high-resolution SNP-mapping in large population samples can detect and fine map quantitative trait loci even if locus specific heritabilities are small. (**Circ Res. 2005;96:693-701.**)

Key Words: arrhythmia; cardiovascular genomics; ECG; quantitative trait locus

Effects of aspirin, clopidogrel and dipyridamole administered singly and in combination on platelet and leucocyte function in normal volunteers and patients with prior ischaemic stroke

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Summary
The aim of this study was to assess whether triple antiplatelet therapy is superior to dual and mono therapy in attenuating platelet and leucocyte function.Aspirin (A), clopidogrel (C), and dipyridamole (D) were administered singly and in various combinations (A, C, D,AC,AD, CD,ACD), each for two weeks (without washout) to 11 healthy subjects and to 11 patients with previous ischaemic stroke in two randomised multiway crossover trials.At the end of each two-week period platelet aggregation, platelet-leucocyte conjugate formation and leucocyte activation were measured *ex vivo* blinded to treatment. Platelets were stimulated with collagen; additional measurements were made with adenosine diphosphate (ADP), platelet activating factor (PAF), adrenaline and the combination of →ADP, PAF and adrenaline. Results show that in the presence of collagen,ACD was superior to all antagonist or combinations, except AC, in reducing aggregation, platelet-leucocyte conjugate formation, and monocyte activation (all $p<0.05$). ACD was also more potent than other treatments, except AC, in inhibiting the aggregation and platelet-monocyte conjugate formation induced by the combination of ADP, PAF and adrenaline.The effects were similar in both volunteers and stroke patients. No serious adverse events or major bleeding events occurred. Triple antiplatelet therapy did not appear to be more effective than combined aspirin and clopidogrel in moderating platelet and leucocyte function.Any additional clinical benefit provided by dipyridamole may be through other mechanisms of action.

Keywords: Aspirin, clopidogrel, dipyridamole, platelets, ischaemic stroke

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The ABO blood group genotype and factorVlll levels as independent risk factors for venous thromboembolism

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Summary
Factor VIII (FVIII), von Willebrand factor (vWF) and the ABO blood groups have been associated with thrombosis.The ABO locus has functional effects on vWF and FVIII levels and is genetically correlated with FVIII,vWF and thrombosis.We carried out a case-control study to assess the role of FVIII, vWF and ABO types on thrombotic risk.We analyzed 250 patients with venous thrombosis and 250 unrelated controls. FVIII, vWF and other factors related to thrombophilia were measured,ABO groups were analyzed by genotyping. FVIII and vWF were higher in non-O individuais. Group O was more frequent in the controls (44.3% v 23.3%; difference 21.1%; 95% CI:13.0—29.3%) and Group A in patients (59.2% v. 41.5%; difference 17.7%, 95% CI:9.1–26.4%),Individuais carrying the A1 allele had a higher risk of thrombosis (OR 2.6; 95% Cl, I.8–3.8).The risk attributed to vWF disappeared after adjusting for

the ABO group. Patients with FVIII above the 90th percentile had a high thrombotic risk (adjusted OR 3.7;95%CI,2.1–6.5), and a high risk of recurrence (OR 2.3; 95% CI: 1.3–4.1). In conclusion, high FVIII leveis and non-O blood groups,likely those with theA1 allele, are independent risk factors for venous thromboembolism and should be considered in evaluating of thrombophilia.

Keywords: Factor VIII, ABO genotypes, von Willebrand factor, venous thrombosis, thrombophilia

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