Molecular and cellular components of human carotid artery plaque related to thrombogenicity
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Atherosclerosis is a dynamic progressive disease of the large arteries characterized by accumulation of lipids, inflammatory and smooth muscle cells (SMCs) and extracellular matrix. In situ growth or embolization of arterial thrombi following a plaque rupture may lead to acute coronary syndrome and stroke. Fibrous cap rupture may expose thrombogenic material, initiating platelet aggregation and coagulation pathways. These thrombotic changes result from activation of the clotting cascade by tissue factor (TF) and coagulation contact phase. Aim of the project is to study Carotid Plaque (CP) thrombogenicity and the vascular wall components responsible for thrombus formation. CP (n=12) from patients submitted to endarterectomy for significant stenosis and internal mammary artery fragments (n=4, controls not atherosclerotic) from individuals undergoing coronary artery bypass surgery were snap-frozen and sectioned. Thrombogenesis induced by CP was evaluated ex vivo under flow conditions using healthy volunteer blood drawn into citrate anticoagulant. Recalcified blood was perfused over CP cryosections at constant flow velocity and 37 °C, and the volume of platelet aggregates and fibrin deposited onto the surface was measured in real time by confocal videomicroscopy. The areas with same XY coordinates than those analyzed in blood flow experiments were relocalized in serial cryosections, to identify by histology (Movat’s, Hematoxylin/Eosin) and confocal microscopy the vascular cell phenotypes and wall components involved in thrombus formation. Thrombi formed mainly over endothelium/intima layer (including fibrous cap); were abundant in the media rich in SMC and in foam cells, in the presence of FSP1, collagen type I, proteoglycans, fibrinogen and TF. The fibro-necro-calcific core was quite unreactive, except when TF was present. IMA wall layers were reactive with analogous pattern but showed a different amount of thrombus formation. Addition to blood before perfusion of anti-human TF monoclonal antibody, or antibody blocking factor XI activation, or a combination of them reduced the volume of platelet aggregates, and of fibrin to a different extent in the different vascular layers. These data suggest an in-situ role of vascular cells and matrix, as well as of intra-tissue TF in thrombus formation over CP, involving both TF and contact phase coagulation pathways.

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