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Hypercoagulability promotes plaque stability via PAR-1 activation on monocytes

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Enhanced coagulation activation is generally perceived as being detrimental for cardiovascular disease. This perception stems from the well known and well established detrimental role of enhanced coagulation activation leading to the formation of occlusive blood clots during acute vascular events, e.g. myocardial infarction. However, atherosclerosis is a slow progressing disease characterized by vascular remodelling, repetitive intraplaque bleeding and thrombosis, and intraplaque accumulation of monocyte derived macrophages. The role of the coagulation system during the chronic phase of the disease, also known as atherogenesis, is less well defined. Clinical studies failed to provide clear evidence for a proatherogenic role of hypercoagulability. This is in contrast to the well-established detrimental role of hypercoagulability and thrombin during acute atherosclerotic complications. These seemingly opposing data suggest that hypercoagulability might exert both proatherogenic and antiatherogenic effects.To study the effect of hypercoagulabilty during de novo atherogenesis two mouse models with hyperlipidemia and genetically imposed hypercoagulabilty were utilized. In both mouse models, hypercoagulability resulted in larger plaques, but vascular stenosis was not enhanced secondary to positive vascular remodeling. Importantly, plaque stability was increased in hypercoagulable mice with less necrotic cores, more extracellular matrix, more smooth muscle cells, and fewer macrophages. Long-term anticoagulation reversed these changes. The reduced frequency of intraplaque macrophages in hypercoagulable mice is explained by an inhibitory role of thrombin and protease-activated receptor-1 on monocyte transendothelial migration in vitro. This is dependent on phospholipase-Cß, phosphoinositide 3-kinase, and nitric oxide signaling in monocytes but not in endothelial cells.It has previously been shown that minocycline can compensate for the lost of the endothelial blood coagulation regulator thrombomodulin (TM) in diabetic nephropathy. Considering the potential role of TM during atherogenesis this raises the question whether minocycline likewise interacts with TM-dependent mechanisms during atherogenesis. Minocycline has previously been shown to reduce neointima formation following vascular injury through an unknown mechanism. The reduction of VSMC number after vascular injury can not be explained by minocycline`s antiapoptotic effects and raises the question, whether minocycline regulates VSMC proliferation. Within in second part of this study minocycline´s effect during de novo atherogenesis were evaluated as to determine whether minocycline directly regulates VSMC proliferation, thus modulating cell numbers independently of apoptosis. To study the effect of minocycline during de novo atherogenesis ApoE-/- mice receiving a high fat diet (ApoE-/- HFD) with or without minocycline treatment were analysized. Minocycline reduced plaque size and stenosis in ApoE-/- HFD mice. This was associated with a lower number and less proliferation of VSMC, reduced PAR (poly ADP-ribosylation) modification and increased p27 expression within the plaques. In vitro minocycline reduced proliferation, PARP-1 expression, PAR modification, and increases p27 expression in VSMC both in the presence and absence of LDL. However, minocycline did not change the frequency of intraplaque macrophages. The data presented in this study, suggest a new function of the coagulation system, averting stenosis and plaque destabilization during de novo atherogenesis. The in vivo and in vitro data establish that thrombin-induced signaling

via PAR-1, Pl-Cß, PI3K, and NO in monocytes impairs monocyte transendothelial migration. The enhanced plaque size observed in mice with hypercoagulability may be in part reversed by treatment with minocycline, as minocycline inhibits proliferation of VSMC, PARP-1 expression, PAR generation and induces p27 expression. Minocycline may be a useful therapeutic adjunct for the prevention or treatment of atherosclerosis, partially reversing the effects of impaired endothelial TM activity by reducing the plaque size. However, while reducing the plaque size, minocycline may promote plaque instability, consisting with a reversal of hypercoagulability triggered effects. Thus, interventions with minocycline may require adjunct therapies, e.g. statins.