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Role of ITAM receptors in thrombosis

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Thrombosis is a major health problem. Arterial thrombosis underlies such diseases as myocardial infarction and stroke. Venous thromboembolism (VTE) causes more deaths than breast cancer, acquired immunodeficiency syndrome and road traffic incidents, combined. However, mechanisms of thrombus development are still incompletely clear. Glycoprotein VI (GPVI) and CLEC-2 represent a family of immunoreceptor tyrosine-based activation motif (ITAM)-containing receptors. We investigated role of these receptors in thrombosis utilizing laser injury in cremaster muscle and a murine model of DVT based on stenosis of the inferior vena cava (IVC). Mice deficient for GPVI had a trend to decreased DVT incidence similarly to mice with antibody-depleted receptor. In the laser injury model, thrombi GPVI-deficient mice began to appear, but did not grow and quickly embolized. The resulting thrombus size was substantially less than in wild-type controls. In contrast, mice lacking CLEC-2 had normal thrombosis in the laser injury model, but were completely protected against DVT. Staining for the CLEC-2 ligand podoplanin did not reveal its expression after 48 h IVC stenosis. Using intra-vital microscopy of the IVC 6 h after application of stenosis we showed that platelet recruitment to the vessel wall was reduced. This implies suppressed endothelial activation and secretion of Weibel-Palade bodies, processes indispensable for DVT in this model. Bleeding time in CLEC-2 deficient mice was comparable with wild-type controls. In conclusion, we report here dissimilar functions of ITAM receptors in different models of thrombosis. CLEC-2 is implicated in DVT whereas GPVI is important for thrombus propagation in the laser injury model.

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Role of reactive oxygen species in insulin resistance and development of atherosclerosis

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Insulin resistance at a whole body level and in the endothelium is shown to be a hallmark of Type 2 diabetes. Insulin resistance in the endothelium reduces bioavailability of nitric oxide (NO), which is well established for its anti-atherosclerotic effects on the vasculature. The molecular effects of perturbations in insulin sensitivity particularly in the endothelium have not been widely investigated. We studied different models of insulin sensitivity and its effects in mediating atherosclerosis and cardiovascular complications. Different experimental models of insulin resistance at a whole-body level and specific to the endothelium demonstrated that insulin resistance eventually leads to an increase in generation of reactive oxygen species and accelerated atherosclerosis via the insulin receptor signaling pathways. These mice have also demonstrated impaired acetylcholine-induced aortic relaxation. This impairment could be reversed by NADPH oxidase inhibitors suggesting a role of reactive oxygen species in mediating insulin resistance and endothelial dysfunction.

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