Coagulation factor Xa as driver of cardiovascular diseases

Summary

Hemostasis is a sophisticated and well-orchestrated interplay between platelets and the coagulation system to prevent blood loss after injury. A dis-balance in this system can lead to thrombosis or bleedings. However, over the past two decades experimental work has shown that proteins of the coagulation system also modulate various other processes beyond their role in hemostasis. In this thesis, I describe the role of factor Xa (FXa; one of the central enzymes in coagulation) in atherosclerosis, myocardial infarction, and atrial fibrillation. To study FXa I often used the clinically available anticoagulant rivaroxaban which is a direct inhibitor of FXa.

Chapters 2 and 3 provide general background information regarding the pleiotropic actions of coagulation proteins. *Chapter 2* dives deeper into the signaling functions of the two central enzymes of coagulation, FXa and thrombin, via protease activated receptors, and how activation of these receptors by coagulation proteins can alter multiple biological processes.

Chapter 3 focuses on the role of coagulation FXa in multiple cardiovascular diseases that have an inflammatory component since FXa is known to promote inflammation. This chapter provides an overview of the downstream pathways of FXa that are potentially indirectly targeted by rivaroxaban.

Chapter 4 elaborates on the role of FXa. In this chapter we intervened with atherogenesis by inhibiting FXa with rivaroxaban. In a prevention study we found that the addition of this anticoagulant to atherosclerosis prone mice, decreased atherosclerotic burden and stabilized the plaque. In an intervention study with atherosclerotic mice, we even showed that FXa inhibition promoted the regression of highly progressed atherosclerotic lesions. Given the lack of optimal atherosclerotic treatment options, this finding potentially has clinical implications.

Given the importance of elucidating the mechanisms that drive FXa inhibition mediated atheroprotection, we unbiasedly studied gene expression after rivaroxaban treatment in atherosclerosis prone mice. In *chapter 5* we show that FXa inhibition influences a large set of different genes related to cellular metabolism: genes belonging to pathways of fatty acid metabolism were mostly upregulated after rivaroxaban treatment. We also show that different processes play a role in early versus late atherosclerosis and that FXa inhibition can have different outcomes depending on the stage of the disease.

Chapter 6 provides four biomarkers that can predict cardiovascular events in patients suffering from peripheral arterial disease. IL-6 was among the predictive markers of cardiovascular events and is a known predictor. Novel predictors of cardiovascular events and mortality included PAR-1, Gal-9 and TNFRSF11a.

In chapter 7 we tested the role of FXa during myocardial ischemia reperfusion injury. Just two bolus injections of the FXa inhibitor rivaroxaban attenuated myocardial cell death and induced long-lasting changes in protein expression.

During ischemia, a timely reperfusion of the tissue is needed to circumvent cell death, and therefore biologically, the formation of new blood vessels is imminently needed. We showed that FXa inhibition promotes a long-lasting increase in proteins involved in the formation of new blood vessels and thereby potentially contributes to cellular protection during ischemia reperfusion injury.

Chapter 8 tested the role of increased coagulation activation in the progression of atrial fibrillation. To study this, a large subpopulation of patients with atrial fibrillation had been followed for 2.5 years with continuous heart rhythm monitoring. We could show that hypercoagulability can predict progression of AF and that mainly the extrinsic route of coagulation, being tissue factor in complex with FVIIa, is responsible for enhanced FXa and thrombin activity during atrial fibrillation progression.

Chapter 9 and 10 contain the thesis summary and general discussion. Here, I put the experimental findings in context and look ahead for avenues of further research and translation.