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Primed to act

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Venous thrombosis is the third most common cardiovascular disease in the Western world after coronary artery disease and stroke [1]. It is a prevalent illness and it occurs in 1 per 1000 persons per year and in 1 per 100 people over 75 years old per year (source: Dutch Heart Foundation). Venous thrombosis is a serious condition that can lead to a life-threatening complication known as pulmonary embolism. Presently used treatments for venous thrombosis increase risk of bleeding in patients. Therefore, scientific research on the mechanisms of venous thrombosis and the development of novel treatment options will be beneficial for thrombosis patients.

In order to perform research that provides directly applicable results and has a notable impact on society, scientific knowledge is needed. The knowledge is developed by fundamental research, the purpose of which is to improve our understanding of natural phenomena without necessarily finding solutions to practical problems. In other words, it is essential to acquire knowledge prior to finding ways how to use it for the benefit of society.

The work described in this thesis is an example of fundamental research. It has previously been discovered in population studies that people who have low levels of an alternatively spliced variant of fibrinogen γ' are at higher risk for venous thrombosis. Also, it has been shown that this form of fibrinogen specifically binds to thrombin exosite II and modulates thrombin activity. Our aim was to understand which of thrombin's functions are affected by fibrinogen γ', in order to get more insight in the association between low levels of fibrinogen γ' and risk for venous thrombosis.

First, we found that a peptide that resembles the C-terminal end of fibrinogen γ', which contains the thrombin exosite II-binding site, inhibits FV activation by thrombin. This, together with its previously described ability to inhibit FVIII activation, underlies the ability of fibrinogen γ' (peptide) to increase APC sensitivity of plasma. This effect is important, as APC resistance is the most common risk factor for venous thrombosis in Caucasians [2]. Since the causes of APC resistance are manifold, there is no specific treatment for this condition. The fibrinogen γ' peptide does not influence FVa and FVIIIa to make them more sensitive to the inactivation by APC. Instead, it inhibits their production, making it easier for APC to down-regulate their activity. Therefore, the

fibrinogen γ' peptide could be a universal solution to counteract APC resistance irrespective of its cause.

Antithrombotic medications that are currently used for treatment and prevention of thrombotic disorders increase the risk of bleeding, since they interfere with processes required for normal hemostasis. It is obvious that new anticoagulants that act on different components of the coagulation system are needed. FXI has recently become an attractive target for the development of alternative anticoagulant therapies, as decreasing its level and activity reduces the risk of venous thrombosis without increasing the risk of bleeding [3]. An antisense oligonucleotide decreasing FXI levels in a dose-dependent manner has been reported to be effective in reducing the risk of postoperative thrombosis without increasing bleeding in a clinical study with 300 patients [4]. These data support the efficacy and safety of anti-FXI approaches as a basis for developing pharmacologic strategies. Similarly, our finding that the fibrinogen γ' peptide inhibits thrombin-mediated FXI activation can also contribute to its therapeutic potential.

The advantage of the peptide compared to the whole fibrinogen γ' molecule is that the peptide has only the effects of binding to the exosite II of thrombin, and not the undesired effects of the whole fibrinogen γ' molecule on fibrin clot structure. In addition, since the peptide has the same amino acid sequence as the C-terminal end of fibrinogen γ', it is not foreign to the human body and will not induce immune reactions. The fibrinogen γ' peptide increases plasma APC sensitivity and inhibits FXI activation, making it an interesting means for future pharmacological interventions.

In fact, a company that develops treatment and diagnostic tools based on the specific properties of fibrinogen γ' already exists. Among other products, a next generation anticoagulant based on the fibrinogen γ' C-terminal end peptide, is being developed [5].

We strongly believe that the findings described in this thesis will help advancing the development of novel anticoagulants.

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