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Quantification and evaluation of the anticoagulant activities of protein S in plasma

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Valorization

According to the World Health Organization (WHO), cardiovascular diseases (CVD) represented about 31 % of all mortalities in the world and affected about 18 million persons around the world in 2015. Venous thrombosis including deep vein thrombosis (DVT) and pulmonary embolism (PE) is considered the third most common cardiovascular disease in the western population following coronary artery disease and stroke with estimated incidence of 1 per 1000 persons per year. Rates increase with age to 1 per 100 persons in elderly people over 75 years old [1]. Venous thrombosis is a threatening disease with major outcomes of death, post-thrombotic syndrome and recurrence and bleeding complications due to use of anticoagulant therapy. For the prevention and treatment of cardiovascular disease, clinical and applied research has to be conducted in parallel with fundamental research in order to provide the basic knowledge which is needed to find diagnostic and therapeutic solutions and eventually lead to improvements in health care and quality of life thereby serving a major societal need.

Currently available antithrombotic treatments increase the bleeding risk in some patients. Therefore, more scientific research and more studies are needed to investigate and understand the biological mechanisms related to blood coagulation in order to find effective diagnostic and therapeutic solutions for patients with venous thrombosis.

The connection between curiosity-driven and translational research is of key value to this PhD project. The content of this thesis provides insight into the natural anticoagulant properties of protein S and its biological variants as a result of basic research. In addition, as a result of applied research, in this thesis new functional assays are presented for the measurement of protein S activity in plasma which can be used as a reliable tool for the diagnosis of protein S deficiency.

Protein S activity assays used in the diagnosis of protein S deficiency are based on measuring APC cofactor activity of protein S, and in a recent study [2] it was shown that the FV Leiden mutation and anticoagulant medication can interfere with the outcome of these assays. Therefore, we used calibrated automated thrombography to develop new functional assays that enable selective quantification of both the APC and TFPI cofactor activities of protein S in plasma which are not affected by the presence of the FV Leiden mutation. The assays yielded reliable quantification of protein S activity and could discriminate be-

tween protein S deficient plasma samples and plasma samples with normal protein S activity. The assays also reliably perform when applied to various types of acquired protein S deficiency. Although our assay is currently only available as a research tool, optimization and simplification of the assay could lead to a novel commercial assay that could replace the current functional protein S assays.

In the present thesis we also investigated regulation of protein S activity by proteolysis and binding to C4BP and showed that cleaved protein S retains full TFPI cofactor activity but is not active as cofactor of APC and that C4BP-bound protein S is partly active both as APC and as TFPI cofactor.

In addition, we showed that protein S-dependent down-regulation of thrombin generation at low as well as high TF is greatly dependent on plasma concentrations of APC and TFPI. Since protein S deficiency is associated with a decreased plasma level of TFPI [3], these findings suggest that the thrombosis risk of protein S-deficient patients is amplified by the low TFPI plasma levels.

In all, these findings are valuable additions to our basic knowledge about biological activity of protein S variants and could aid in further unraveling of the mechanistic properties of protein S leading to a better understanding and prevention of thrombotic disease.

References

1. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J. Thromb. Haemost. 2007;5:692–9.

2. Smock KJ, Plumhoff EA, Meijer P, Hsu P, Zantek ND, Heikal NM, et al. Protein S testing in patients with protein S deficiency, factor V Leiden, and rivaroxaban by North American Specialized Coagulation Laboratories. Thromb. Haemost. 2016;116:50–7.

3. Castoldi E, Simioni P, Tormene D, Rosing J, Hackeng TM. Hereditary and acquired protein S deficiencies are associated with low TFPI levels in plasma. J. Thromb. Haemost. 2010;8:294–300.