

Preface

Tissue Factor in Arterial and Venous Thrombosis: From Pathophysiology to Clinical Implications

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The history of tissue factor (TF) goes back to the early 1960s with the discovery of brain thromboplastin and the documented evidence of its role in blood coagulation.¹ Since 1987 several studies have documented the presence of this protein within human normal and pathological tissues, focusing on atherothrombotic diseases and cancer.^{2,3} Since the beginning of the new millennium, this scenario has been intensely studied.

TF is a 47-kDa glycoprotein that binds to activated factor VII (FVIIa), leading to activation of factor X (FX) and factor IX (FIX). TF-initiated coagulation is fundamental in inducing thrombosis in the arterial and venous compartments. Tissue distribution reveals that TF is expressed in perivascular tissue, resulting in rapid hemostasis upon vascular injury. In addition, TF is present within atherosclerotic plaques mostly associated with macrophages and smooth muscle cells. TF is not normally present within the circulating blood, but its expression can be induced in monocytes and neutrophils by a variety of agonists. Also, platelets have been recently shown to express TF upon activation. In addition, circulating microparticles (MPs) can provide consistent amounts of TF.^{4,5}

This issue of *Seminars in Thrombosis & Hemostasis* is focused on the role of TF in arterial and venous thrombosis, providing insights that span from pathophysiology to clinical implications. First, Gajsiewicz and Morrissey review the structure–function relationship of the interaction between TF and FVIIa, providing insights into their mechanistic activities in several biological processes.⁶ These concepts are extended to novel noncoagulant signaling mechanisms for the TF/VIIa complex, as cell migration and apoptosis, as pointed out by Åberg et al.⁷ Apart from cell- and vessel-wall associated TF, the pathophysiological role of noncell-associated, and specifically of soluble, TF is addressed by Bogdanov and Versteeg.⁸ Cimmino et al then review the role of TF in coagulation and atherothrombosis, underlying the different mechanisms by which TF modulates this com-

plex network that comprises not only blood coagulation but also other processes, for example, intracellular signaling, proliferation, and angiogenesis.⁹ Of particular interest nowadays is the role of TF-bearing circulating microparticles; although some methodological aspects still need to be solved, their application as prognostic biomarkers in venous or arterial thrombosis is very promising, as highlighted by van Es et al.¹⁰ Neutrophils, which also express TF, may be physiological regulators of intravascular thrombosis, besides being the first line of defense of the immune system, as reviewed by Maugeri and Manfredi.¹¹ In addition, a role of platelet TF can be proposed in patients with cardiovascular disease as highlighted by Camera et al.¹² In particular, the fate of TF starting from the megakaryocyte up to the mature platelet is described. The articles by Versteeg and Falanga et al focus on the role of TF on cancer progression and on its relevance as a biomarker to assess the thrombotic risk in patients with cancer.^{13,14} Finally, Chiu et al review the role of protein disulphide isomerase (PDI) in thrombosis and discuss the proteins, including TF, characterized as PDI substrate.¹⁵

Moving from TF, in the last part of the issue, three contributions focus on the use of new oral anticoagulants as well as new hemostatic agents. No gender-related differences in safety and efficacy of direct oral anticoagulants (DOACs) are reported by Dentali et al in patients with atrial fibrillation (AF) or acute venous thromboembolism (VTE), with only a trend toward an increase in risk of bleeding in males as compared with females in the extended treatment of VTE.¹⁶ Increased bleeding is a major issue in the treatment with oral anticoagulants. In particular, Franchini et al review the management of bleeding associated with the use of DOACs, providing physicians with an algorithm for managing DOAC-associated bleeding.¹⁷ Finally, Franchini et al summarize new technologies and the current development status of the novel products for hemostasis, focusing in particular on

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those with half-life extension for the treatment of hemophilia.¹⁸

All the authors of this issue are thanked for their comprehensive contributions showing unique insights into TF and other aspects of thrombosis and hemostasis, and it is hoped that the readership finds interest in this issue of *Seminars in Thrombosis & Hemostasis*.

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