

Can Tissue Factor, A Multifactorial Molecule of the Hemostasis, be used As A Biomarker for Thrombosis, Inflammation and Cancer?

Nesrin Emekli^{1*}

¹Division of Biochemistry Faculty of Medicine, Medipol University, Istanbul, Turkey

ABSTRACT

Tissue factor (TF) is a transmembrane protein found in many tissues and is active in various biological reactions. It is a member of the cytokine receptor superfamily and is referred to as CD 142 because of this feature. TF is also known as Factor III in the coagulation system and binds FVII/VIIa. The TF and FVIIa complex has both procoagulant and signaling activities. It functions in many biological processes, including hemostasis, thrombosis, inflammation and cancer. TF is essential for haemostasis but increased TF expression within atherosclerotic plaques and TF positive microparticles were detected in thrombotic conditions. TF increases inflammation by enhancing intravascular fibrin deposition and activates protease-activated receptors (PARs). TF and FVIIa complex also contribute to tumor growth by activating PAR2. Recent retrospective studies have shown that TF positive microparticles increase in the plasma of cancer patients. Therefore TF may be suggested to be used as a biomarker. However further studies are required to reveal the availability of TF as a biomarker to identify cancer and risk of thrombosis and inflammation.

Keywords: Tissue Factor, Hemostasis, Thrombosis, Inflammation, Cancer

INTRODUCTION

Hemostasis, which allows blood to circulate without clotting, allows bleeding to stop through a rapid response to tissue damage. A clot is formed through reactions involving blood vessels, thrombocytes, coagulation and fibrinolytic system, which then bleeding stops and dissolves the fibrin clot.¹⁻⁵

The work of hemostasis in a vascular damage is summarized as follows: 1-The artery in the region is vasoconstricted, the purpose is to slow the blood flow through the re-

*Corresponding author: Nesrin Emekli
E-mail address: nemekli@medipol.edu.tr

gion, 2-Circulating thrombocytes recognize endothelial damage, apply adhesion, secretion and aggregation, therefore rapidly forming a weak clot, 3-The coagulation proteins in the circulation recognize that they've encountered an environment different than the endothelium, and intact clots form in the interrupted region, 4-The fibrinolytic system helps repair the injured area, allowing the fibrin to break down and the blood flow in the area to return to normal. In this system, clotting is simultaneously created and prevented. The blood running in a vessel does not coagulate but immediately it coagulates when encounters a foreign surface such as tissue factor and collagen. Endothelial cells play a major role in stopping a bleeding and preventing thrombus formation. ⁶⁻¹¹

The mechanism of partial thromboplastin time (PTT) and prothrombin time (PT) tests used in the follow-up of diagnosis and treatment of bleeding and coagulation-related diseases is clotting when blood encounters non endothelial surface.¹² This mechanism is important for arterial thrombus formation. In summary, it is not wrong to say that the formation of blood clots in endothelial dysfunction is not well managed.

The hemostatic system parameters continue to be at the center of scientific research with unknown aspects, while providing opportunities to facilitate diagnosis and treatment on bleeding and thrombosis events. As in the past, the incidence of thrombosis in arterial and venous circulation is currently very high. Atherosclerotic cardiovascular and cerebrovascular diseases are still major causes of morbidity and mortality worldwide. ¹³⁻¹⁷

Tissue factor, which is present as Factor III in the clotting pathway and also known as "CD 142" and "thromboplastin", is a transmembrane protein which enables thrombin formation and is multifunctional. Parallel to today's technology, there are many studies aiming to better know the structure of tissue factor, while reporting that this protein is not only effective in the clotting system, but also in inflammation and cancer formation. ¹⁸⁻³³

The purpose of this article is to draw attention to how some phases of hemostasis developed historically and encourage young researchers to shine a light on the unknown aspects of this subject.

Historical development of and current knowledge on hemostasis

The hypothesis that the German physician Rudolph Virchow, who lived between 1820 and 1902, which corresponds to the thrombosis aspect of present-day hemostasis;

1-Intravenous wall change (thrombosis due to atherosclerotic change, inflammatory change)

2-Change of blood components (hypercoagulability, thrombocyte activation, anticoagulant insufficiency)

3- It is in the form of blood flow alteration (Deep vein thrombosis and pulmonary embolism)

Numerous additions have been made to this hypothesis through scientific studies in parallel with the development of technology, but Wirschoff's thrombus formation hypothesis still remains valid (13,18-13).

Thrombocytes in Hemostasis

1842 is considered as the year of birth for thrombocytes. Because in those years, four different researchers, unaware of each other, reported that a different particle was circulating differently from erythrocytes and leukocytes. In 1846, Zimmerman noticed that these particles formed aggregates. The following rapid developments in these studies have led to a better understanding of the role of thrombocytes in hemostasis. In 1956, Ulutin and Karaca first announced to the world the mechanisms of secretion of thrombocytes, and that disorders in this mechanism would cause a disease^{1-2,34-42}

Coagulation Proteins and Tissue Factor (CD 142)

The foundations of the coagulation mechanism were laid in 1834. In those years, brain tissue suspensions were found to be immediately lethal when administered intravenously to animals. This finding led to the understanding that tissue extracts formed clots in blood. Tissue factor had a place in Schmidt's works in 1892 and in Morawitz's work in 1904 and tissue factor, prothrombin and fibrinogen were all portrayed in the simple mechanism of the coagulation system. After the year 1900, the studies focused on the tissue factor of clotting mechanism for a long time. Works to purify tissue factor started in 1912 with Howell, and in 1944 with Chargaff et al. Studies on this purification of tissue factor continued until the beginning of 1980s. Later studies were rather on the genetics of tissue factor. At the end of the 1980s the tissue factor gene was isolated and cloned. From the 1990s onwards, tissue factor was considered to be a real initiator in the coagulation system. Among 13 clotting proteins, only the tissue factor is an integral membrane protein. Clotting factors exhibit structural homology, while only the tissue factor exhibits homology with type 2 cytokine receptors. For this reason, tissue factor was also named as "CD 142".^{18-33, 43}

Tissue factor, a transmembrane protein, is present in various proportions in all tissues, mostly in the brain, lung, and uterus. The tissue factor contains protein, phospholipid and carbohydrate in varying proportions according to the tissue from which it is obtained. The carbohydrate portion of the tissue factor is added

by posttranslational modification. Tissue factor is a cofactor for Factor FVII in cell membranes. It is comprised of 263 amino acids in total. 219 of these amino acids are located in the extracellular region, 23 amino acids in transmembranal regions and 21 amino acids are in intracellular regions. The extracellular region of the tissue factor contains the binding site for Factor VII. ¹⁸⁻³³

In 1947 Owren reported that Factor V was necessary for the formation of the clot and this invention was followed by other coagulation proteins. Concerning the conversion of prothrombin to thrombin, Prof. Dr. Walter H. Seegers' intensive studies and contributions from other researchers led to significant advances in clotting mechanisms between 1905-1950. The identification and mechanism-description of the 13 clotting proteins present in the present coagulation pathway, expressed as "clotting factors", were carried out by Davie and Ratnoff in 1964 (36). The current flow chart of the intractable coagulation system has emerged from the examination of patients with bleeding findings with clotting defects. ^{13, 43-46}

The Prothrombin time test, administered by Quick in 1935, remains among today's gold standards in the control of the clotting system ⁴ In our faculty, Medical and Dental Practice students in the 1st grade isolate tissue factor from the bovine lung and use it in the prothrombin time test. The students presented this study in İstanbul Medipol University "Student Scientific Days" in 2015 and received a runner-up prize ⁴⁷ Figure 1 shows the prothrombin time test's flow diagram.

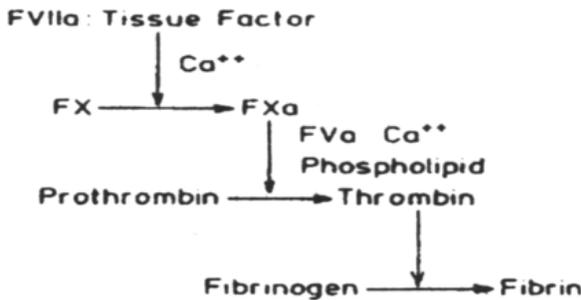


Figure 1. Biochemical reactions take place in the prothrombin time test (Ref.12)

Tissue Factor and Thrombosis

Adverse changes leading to thrombus formation in the blood stream begin with hypercoagulation and endothelial activation. Wirschoff explains the reasons for the thrombus that still remain valid today with the possibilities of the 1800's. One of the most important aspects of the present invention is the demonstration of the presence of microparticles bearing a tissue factor. Dimensions of microparticles carrying TF vary between 30-1000nm. Microparticles are released

from activated leukocytes and thrombocytes. Hatemi¹¹ reported that in diabetic and especially type 2 diabetic patients, thrombophilia is observed and that these patients have increased coagulation factors, especially fibrinogen, and also increased thrombocyte adhesion and aggregation, while fibrinolytic activities were observed to be in a decrease. Today, contrary to previous knowledge, the presence of biocompatible tissue-factor-bearing microparticles has been demonstrated and it is predicted that the tissue factor may be a biomarker in this area since the importance of arterial thrombus formation is emphasized.^{5-17,26,27,31,48-54}

Is Tissue Factor a Proinflammatory Agent?

Endothelial cells are a common point between coagulation and inflammation. Inflammatory diseases are known to increase tendency to thrombus. In 1936, life-threatening thromboembolic events were seen in ulcerative colitis cases, which were thought to be associated with increased tissue factor. Fibrin deposits are seen in synoviums of patients with rheumatoid arthritis. The extracellular portion of the tissue factor obtained with the recombinant technique was injected into the articulations of healthy mice and 80% of the mice developed arthritis. Studies on which factor to remove for the purpose of preventing the relation between inflammation and coagulation have not yet reached a point of clarity; this subject is still yet to be resolved.^{32, 33, 55-61}

Tissue Factor and Cancer

Patients with cancer are more likely to have thrombosis. The relationship between thrombosis and cancer first began with the observations of Armand Trousseau in 1865. Various studies have shown that tissue factor expression increases in cancerous cells. In physiological conditions, the amount of micro particles bearing tissue factor is low. These particles are seen to increase in cases of cancer. TF plays an important role in development of physiological and pathological angiogenesis. Since TF-deficient transgenic mice had deteriorating vascular integrity, embryogenic death occurred in a short time and abnormal development of embryonic development was observed. Similar histopathologic results were seen in VEGF-deficient embryos. Here it is understood that TF and VEGF act similarly. Proangiogenic and antiangiogenic factors are essential for vessel growth and development. TF shows its effect on tumor growth, metastasis and angiogenesis independently of the clotting system but dependently on clotting. TF indirectly increases angiogenesis and tumor growth in coagulation-independent mechanisms by forming fibrin directly or via thrombin. In the coagulation-dependent case, it is known that increasing TF expression leads to increased fibrin formation.^{28-30, 62-68}

Control in Hemostatic System

Hemostatic system is internally controlled. Minimal thrombin coagulation, which forms out of very small amounts of tissue factor, activates the system by activating proteins and thrombocytes in the coagulation cascade. These effects of thrombin on procoagulants are positive feedback reactions in the system. Thrombin, on the other hand, converts the protein C to the active protein C (formerly autoprothrombin II-A), which is an anticoagulant, with the effect of the protein C receptor (EPCR) and thrombomodulin found in the endothelium. Figure 2 shows positive and negative feedback reactions of the clotting system. That is, the clot formed with minimal tissue factor is neutralized with minimal tissue factor.

Protein C complex, which exhibits anticoagulant activity by inhibiting strong cofactors such as Factor VIII and Factor V in physiological conditions, has not yet been successfully used in therapeutic applications such as heparin. However, both protein C pathway and tissue factor inhibitor pathway (TFPI) are vital in hemostatic control. This anticoagulant, first identified as autoprothrombin II-A by Seegers and colleagues because of its relevance to prothrombin, has then been referred to as “protein C”. Emekli and Ulutin reported that protein C inhibited fibrin production in disseminated intravascular coagulation induced rabbits and the animal model used in this study was the first in the literature.⁶⁹⁻⁸⁴

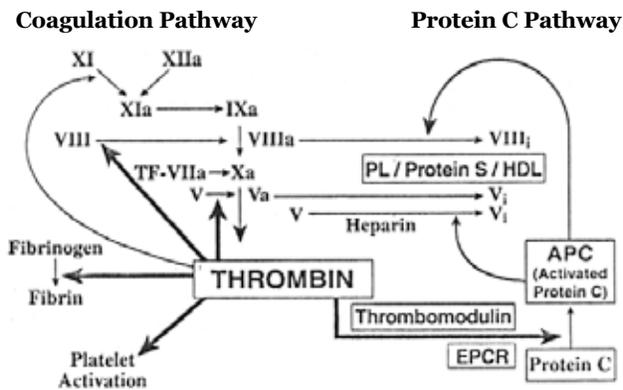


Figure 2: Effect of thrombin on anticoagulant system driven by procoagulant and protein C in the clotting mechanism (Ref.84)

Heparin is a heterogeneous polysaccharide with glucose derivatives and sulphates in its structure. It has been researched since 1800s and is still used as an anticoagulant in treatments.⁸⁵⁻⁸⁶

Prof. Dr. Kasım Cemal Güven, who founded Acta Pharmaceutica Scientia in

1953 and maintained it throughout the years, demanded this Journal be published by İstanbul Medipol University from this year onwards. ⁸⁷⁻⁹⁰

In conclusion, vascular, thrombocyte, coagulation and fibrinolytic systems of hemostasis are a complex reaction sequence containing negative-positive feedback reactions, multienzymes systems, humoral and cellular procoagulant and anticoagulants. Tissue factor (CD 142), which is included in this system and has versatile functions, is a current topic in today's studies in that it can be a biomarker for arterial-venous thrombus, inflammation and cancer.

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