Tissue factor, its biological function and role in the etiology of prostate cancer

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ABSTRACT

Tissue factor (TF) is a substance of great biological relevance. TF activates the extrinsic coagulation cascade and takes part in the mechanisms of inflammation and atheromatosis. TF, through its influence on neoangiogenesis, plays a great, but not exactly recognized, role in the origin and spread of neoplasms, including prostate cancer.

INTRODUCTION

The higher incidence of thromboembolic complications in patients with neoplastic diseases in comparison to healthy population was noticed back in the nineteenth century. The estimated frequency is 10-25% of the population, which signifies the second most common cause of mortality in oncology patients. Initially, this phenomenon was described in 1886 by Armand Trousseau who observed a correlation between colon cancer and superficial thrombophlebitis. This complication involves a grave prognosis. Neoplastic cells are capable of producing a great amount of factors influencing the activation of thrombosis and fibrinolysis. These factors are; tissue factor (TF), neoplastic procoagulant, and plasminogen activators, inhibitors, and receptors. Different therapeutic methods including surgery, chemo and radiation therapy may also influence the processes of hemostasis and fibrinolysis [1, 2, 3, 4, 6].

Tissue factor – structure and function in coagulation mechanisms and other biological processes

Tissue factor (TF) was previously called coagulation factor III. For the first time it was isolated in the 1980-ties, and during the next decade its chemical composition, structure, significance at the cellular level, and its role in biological processes have been extensively studied. Hvatum and Prydz first isolated TF. In 1981 Nemerson and Bach extracted TF from the bovine brain, and in 1985 TF was detected in human brain by Broze [2, 3 ,4].

TF is a transmembrane protein weighing 47 kDa and containing 263 amino acids in molecule. It acts as the receptor for clotting factor VII. Its molecule consists of 3 domains: intracellular, trans- and supramembranic; all of which are engaged in the activities of hemostasis. The gene encoding TF is located on chromosome 1 and consists of 6 exons [1, 2, 3, 4, 5, 6, 7].

TF initiates the extrinsic coagulation pathway. Following vessel injury, the subendothelial structures come in contact with the blood, allowing TF binding to factor VII provoking its activation. This complex of TF/VIIa directly activates factors IX and X, which stimulate conversion of prothrombin into its active form, thrombin. Thrombin influences conversion of fibrinogen into the monomers and then into the fibrin polymers. These processes occur in the presence of calcium ions and under the influence of factor XIII, a stable form of fibrin that builds this factor [1, 2, 3].

TF is found in large amounts in the brain, lungs, kidney, endometrium, skin, and placenta. Significant concentrations can also be found in the endothelium, smooth muscles of the vessel, and in the mucosa of the gastrointestinal tract. TF may also undergo synthesis by monocytes and macrophages under the stimulation of mediators of the inflammatory process: cytokines, antibodies, and endotoxins. It is involved in atherosclerotic plaque formation. TF initiates proliferation and migration of the vascular, endothelial, and smooth muscle cells. Its concentration in serum ranges from 28 to 469 pg/ml, as measured by ELISA [1, 2, 3].

The role of TF in the development of the primary neoplastic focus and metastatic spread

TF can be produced in great amounts by neoplastic cells in a continuous and uncontrolled way. The augmented expression of TF was detected in solid tumors of the pancreas, brain, ovary, breast, and prostate as well as in hematological malignancies, including leukemia. The rise of TF in serum may result from tumor breakdown following chemotherapy, radiation therapy, or surgical procedures. TF influences vessel endothelium proliferation, stimulating its growth by vascular endothelial growth factor – VEGF. VEGF is a primary cytokine, stimulating both physiologic and neoplastic angiogenesis. In neoplastic tumors it contributes to increasing density of vessels, which then lead to growth and progression of the tumor. TF also plays a significant role in adhesion, migration, and invasion of neoplastic cells, which contributes to spread of disease and development of metastases. Thus influencing the natural course of the malignancy as well as determining the patients' rate of survival.

The role of TF in hemostasis in patients with malignancy is described as superficial thrombophlebitis (Trousseau syndrome), deep vein thrombosis, and pulmonary embolism. In many patients with advanced neoplastic diseases, the increased serum markers of disseminated intravascular coagulation (DIC) were detected: fibrinopeptide A, thrombin-antithrombin (TAT) complexes, FDP, and D-dimers. The sudden rise of TF concentration in serum, i.e. following chemotherapy, may culminate in profuse bleeding from injured tissues. It is caused by consumption of coagulation factors following DIC [1, 2, 3, 4, 5, 7].

TFPI

TF has its own specific inhibitor, tissue factor pathway inhibitor (TFPI), a 37 kDa glycoprotein. It is mainly produced by the vascular endothelium, but not by neoplastic cells. Its concentration is high in patients suffering from cancer complicated by thromboembolic events and DIC, especially in prostate, pancreas, gastric, ovarian, breast, and colonic cancers. TFPI inhibits activity of the TF-VIIa complex. Concentration of TFPI rises after unfractionated heparin

injection; heparin also promotes inhibitory function of TFPI on TF-VIIa complex and factor Xa [3].

Role of tissue factor in the development of prostate cancer. Literature review

From the beginning of the nineteenth century, only a few of papers were dedicated to the role of TF in the development of angiogenesis and the natural history of prostate cancer. The authors examined TF level in blood, urine, tissue biopsies, and pathological species obtained after radical prostatectomy. They strived to answer some important questions concerning the previously known function of TF in the development of other types of cancer. Is the TF level (in serum, urine, tissues) significantly higher in patients with confirmed prostate cancer compared to control groups of healthy males? If yes, can any correlation be found between TF, clinical stage, and histopathologic grade of prostate cancer? Can the occurrence and concentration of TF become a significant prognostic factor in prostate cancer? Is there any link between this and the risk of thromboembolic complications in patients suffering from this type of cancer?

Langer and associates studied 140 males with confirmed prostate cancer, clinically confined to the organ, and who were scheduled for radical prostatectomy and operated between January 2002 and March 2003. The patients whose comorbidity or pharmacotherapy may have influenced hemostatic activity or TF level were excluded from the study. The authors examined TF level and other coagulation parameters such as complexes of plasmin-alpha 2-antiplasmin, D-dimers, and soluble ligand CD 40, as well as soluble P-selectin and alfa 2-antiplasmin in blood samples taken before radical prostatectomy. Results were then compared to clinical parameters and histopathologic staging. Patients underwent regular follow-up and the observation period was terminated in 2006 with assessment of the percentage of cancer recurrences and their correlation with TF concentration. Out of a total of 140 patients included in the study, 81% had a concentration of serum TF exceeding 40 pg/ml and 23% of the patients demonstrated a TF level of 200 pg/ml, where the mean value was 107 pg/ml. In the control group of 42 males, concentration of TF level greater than 40 pg/ml was found in only one patient (2%). Thus, preoperative concentration of TF was considerably higher in patients suffering from prostate cancer. The difference was statistically significant. The authors did not find a statistically significant correlation between the preoperative level of TF and the clinical and histopathological parameters of prostate cancer such as preoperative PSA level, clinical stage, and histopathological grade according to Gleason. They did however observed a correlation between serum D-dimer level and histopathological differentiation grade. Patients with high and moderate grades (in Gleason's classification up to 6th grade) and patients with cancer confined to the prostate had a lower D-dimer level than patients with poorly differentiated (Gleason >6) or locally advanced (pT3) cancer. One-hundred thirty-two patients, out of the 140 initially enrolled, have completed 4-year follow-up. In 17 cases cancer recurrence, defined as PSA rise above the 0.1 ng/ml level, was observed. In the same group, mean preoperative TF level was 161 pg/ml compared to 105 pg/ml in all cured patients. This difference can hardly be considered as statistically significant because 21% of patients had a preoperative level exceeding 200 pg/ml [4, 5].

Utilizing ELISA, Yvonne Foster and associates measured TF level in serum and tissues obtained from postoperative specimens of prostate, bladder, and kidney cancers. The blood samples were taken from 157 prostate cancer patients and 92 healthy volunteers. The authors did not find a statistically significant difference in TF concentration in neither of the evaluated groups. Also, in patients with kidney cancer, the TF level did not differ significantly from the healthy group. Such a difference (statistically significant) was observed only in the group with bladder cancer. The authors also examined the concentration of TF in extracts from tissues obtained during surgical procedures. The highest TF level was observed in radical prostatectomy samples and the lowest TF level was observed after radical nephrectomy. A statistically significant difference between expression of TF in prostate cancer tissue and normal prostate specimens was not observed [9].

Finding an elevated TF level in the urine of patients with colon and breast cancer prompted a team of researchers, lead by B.A.L. Waleed, to a similar study of patients with prostate and bladder cancer. They assessed 26 patients with confirmed prostate cancer in different stages. The studied group was compared to a group of 67 males with benign prostate hypertrophy (BPH) and 13 males with prostatitis. Fifty percent of patients with proven prostate cancer had scyntigraphically confirmed bone metastases. The authors disclosed an elevated TF level in urine (uTF) from patients with prostate cancer and prostatitis compared to the group of patients with BPH. They concluded a statistically significant correlation between TF level and differentiation grade of prostate cancer. The mean concentration of TF in urine for Gleason's grade 2-4 was 10 ng/ml, in grades 5-7 was 17 ng/ml, and in the low differentiated cancer (Gleason's 8-10) reached 24 ng/ml. The concentration of TF in urine exceeded concurrently with PSA level. Patients with bone metastases had a higher level of TF in urine than patients without metastases. That difference was also statistically significant [6].

A.S. Adamson and associates conducted a similar study on prostate cancer patients. They discovered that the concentration of TF in urine from patients with prostate cancer is significantly higher than in the group of patients with BPH. The authors concluded that the concentration of uTF correlates with the cancer's clinical stage. The patients with bone metastases had a statistically significant TF concentration in urine compared to the group without metastases. The authors did not find a comparable correlation (statistically significant) between uTF and PSA. They also described a significant decline of uTF in patients who underwent a total androgenic blockade [11].

The significance of TF in the occurrence of cancer and development of metastases is related to its role in angiogenesis. This process is controlled by growth of endothelial vessels. TF acts indirectly via VEGF, a by-product of the coagulation process [1]. This phenomenon was the subject of a study by N. Weidner and associates. The hallmark of angiogenesis is the so called microvessel density (MVD), defined as the number of microvessels in a unit area of a prostate biopsy specimen. This index was significantly higher in patients with prostate cancer that had metastasized to bone. According to Gleason, the number of microvessels had also increased with loss of differentiation, which was especially prominent for poorly differentiated cancers. The authors concluded that the high MVD index may be useful in extracting a subgroup of patient requiring aggressive treatment [10].

Research conducted by S.A. Abdulkadir and associates was devoted to study the influence of TF on angiogenesis in prostate cancer. The authors examined the expression of TF in specimens obtained after radical prostatectomy performed in 67 patients who were then subjected to a strict follow-up protocol. The surgical biopsy specimens were incubated in a solution of polyclonal antibodies targeted against human TF. In prostate tissue specimens, the MVD was also measured. The specimens from 67 prostatectomies were examined. In 49 patients (73%) an elevated expression of TF in prostate cancer tissue was found compared to healthy neighboring tissue from the same specimens. The expression of TF was mainly observed in endothelial cells of adenocarcinoma.

The staining of interstitium and normal prostate tissue was minimal. The authors have also tried to answer the question regarding the expression of TF in prostate cancer and clinical and pathological prognostic factors in this type of disease. They were able to show the relation between the expression of TF, preoperative level of PSA, and positive surgical margins. A statistically significant correlation between TF saturation in prostate cancer and the level of cancer differentiation (according to Gleason) was not observed. Similarly, the expression of TF did not influence the risk of recurrence of prostate cancer. The authors also observed a statistically significant correlation between the TF saturation of prostate cancer tissue and the increased number of MVD in the examined tissue, thus confirming the role of TF in the neoangiogenesis process. They also suggested that implementation of TF inhibitors (i.e. antibodies against human TF) may slow the progression of prostate cancer [7].

The similar study was conducted by Japanese researchers under the guidance of T. Akashi. The expression of TF was measured in prostate specimens obtained by transrectal biopsy from 73 patients treated between 1986 and 1999. All patients had bone metastases and all underwent surgical or pharmacological castration. The monoclonal antibodies against human TF were used to assess the TF tissue saturation. In 75% of cases the overexpression of TF in prostate cancer specimens was found. The authors did not observe a statistically significant difference between this parameter and the preliminary level of PSA, differentiation grade according to Gleason, advancement of bone involvement, or response to applied treatment. The authors pointed out that TF was one of the prognostic factors influencing the survival rate in this specific disease [8].

The authors of all papers mentioned above observed that the concentration of TF in blood and urine of patients with prostate cancer was definitely higher than in the healthy population. The level of TF was nevertheless higher in patients suffering from chronic prostatitis and it did not differ significantly from those with prostate cancer. Also, in the prostate cancer specimens, a significantly higher concentration of TF compared to normal prostate tissue was found. This was also related to the higher concentration and increased density of small vessels, which influenced the accelerated growth of the tumor.

Only a small group of researchers was able to prove a statistically significant correlation between TF level and the clinical and histopathological markers of prostate cancer including; PSA level, clinical stage of disease, differentiation grade according to Gleason, and risk of recurrence. TF may act as a useful prognostic factor for estimating disease progression and survival probability in prostate cancer.

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