Participation of fibrin, fibrinogen, and their degradation products in pathogenesis and progression of cancer may lead to complications of thromboembolic events. The tumor may be a source of fibrinogen. Fibrinogen inside the tumor is one of the factors of its growth and metastasis. Fibrinogen, fibrin and their degradation products possess proinflammatory activity. They indirectly stimulate endothelium to secrete von Willebrand factor, leading to activation of platelets accompanying neoplastic disorders. Fragments E and D are the end products of fibrin(ogen) degradation and E and DD are the end products of stabilized fibrin. E stimulates proliferation, migration and differentiation of endothelial cells, contributing to tumor vasculature. Increased levels of DD are observed in malignant neoplasms, such as breast, lung, colon and ovary cancers. In breast cancers DD correlates with progression of disease and metastasis. The role of fibrinogen and the products of its degradation in the progression of various tumors is not sufficiently understood.

**Key words:** fibrinogen, fibrin, tumor, plasmin, metastasis.

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### The role of fibrinogen, fibrin and fibrin(ogen) degradation products (FDPs) in tumor progression

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**Introduction**

The relationship between the occurrence of cancers and coagulation disorders (Fig. 1), leading to thrombosis, was noted as early as in the 19th century. In 1886, Armand Trousseau first described the increased rate of venous thrombosis in patients with tumors of the digestive tract [1]. Nowadays, it is known that participation of hemostatic proteins (including fibrinogen) in the pathogenesis and progression of cancer and subsequent complications goes beyond the thromboembolic complications. The development of cancer disease induces a host response; numerous inflammatory mediators are secreted and disturb the hemostatic balance, leading to the increase of the blood prothrombotic potential. Additionally, activation of the coagulation system is also enhanced by various factors released from transformed cells [2–4]. The increased synthesis of acute phase proteins (including fibrinogen), stimulation of blood coagulation and activation of extravenous proteolysis are not only phenomena associated with neoplasm, but also an integral mechanism of cancer progression [5, 6]. A growing number of reports have confirmed a wide range of biological activities of fibrinogen, fibrin and their degradation products. The physiological activity of these molecules includes not only participation in the coagulation process, but also repair of damaged vessels, stimulation of migration, and proliferation of various cells, angiogenesis and wound healing. Furthermore, fibrinogen and its derivatives affect the contraction and relaxation of blood vessels, stimulate the permeability of capillaries and modulate the activation of blood platelets. Most of these properties of fibrinogen, fibrin and their fragments are particularly important in the biology of developing tumors and actively participate in the progression of cancer [7].

### Molecular structure of fibrinogen

Fibrinogen is a heterohexameric glycoprotein, formed from two sets of three non-identical polypeptide chains $\alpha$, $\beta$ and $\gamma$, interconnected with disulfide bonds (see Fig. 2). The C-terminal domains of $\alpha\alpha\alpha$, $\beta\beta\beta$ and $\gamma\gamma\gamma$ chains of fibrinogen are homologous and consist of approximately 225 amino acid residues. Their physiological functions are similar to the related C-terminal domains in other proteins, such as in angiopoietins, tenascins or ficolins, and include recognizing and binding of various molecules [8]. Two C-termini of $\beta\beta\beta$ and $\gamma\gamma\gamma$ chains of $\beta\gamma$ and $\gamma\gamma$ domains form two terminal D fragments of the fibrinogen molecule, respectively. N-termini of two triples of listed chains overlap in the central part of the whole molecule forming the E fragment. The C-terminus of the $\alpha\alpha\alpha$ chain in isoform II does not show homology to the C-ends of $\beta\beta\beta$ and $\gamma\gamma\gamma$ chains, occurring in the vast pool of human fibrinogen with molecular weight 340 kDa. $\alpha\alpha\alpha$ chains, after turning at fragment D, point in the direction of fragment E, near which unfolded $\alpha\gamma$ domains form [9]. In addition to isoform II, isoform I also is present ($\alpha\alpha\alpha\gamma\gamma$); it can be found in a pool of fibrinogen of 420 kDa and constitutes about 4% of the total human fibrinogen [10]. The appearance of
both isoforms is a result of the alternative splicing of a common gene for the Aα chain. Isoform I is characterized by the C-terminal domain homologous to domains of Bβ and γ chains, but it is shifted in relation to domains BβC and γC (similarly as in the case of isoform II it is located in the vicinity of fragment E) [11]. Chains Aα, Bβ and γ are encoded by separate genes. All these genes are located immediately next to each other on chromosome 4 in humans, but the gene for the Bβ chain is located on the opposite DNA strand, in comparison to the previous two [9]. This occurrence suggests the probable inversion of the gene, relative to the other, after two local duplications leading to isolation of three distinct genes from a common hypothetical ancestor. Furthermore, insertions in the Aα chain led to the shifting of the C-terminus vs. homologous domains of Bβ and γ chains [12]. Aα and Bβ chains have short peptides at the N-termini, A and B respectively. These peptides are cleaved by thrombin as a result of proteolysis of the peptide bond between arginine and glycine, leading to exposure of the polymerization sites A and B in the E fragment, which are complementary to polymerization sites “a” and “b” in the C-terminal domains of γ and β respectively. Consequently, after release of fibrinopeptides, fibrin monomers polymerize and build initially protofibrils, and then a fibrin network. The main fibrinolytic enzyme, plasmin, degrades fibrin into end products such as the D fragment with a molecular mass of about 90 kDa, fragment E of about 60 kDa, and polypeptide fragments A, B and C. If the fibrin is exposed to factor XIII, within γ and α chains, between D fragments of different fibrin monomers covalent bonds are formed and enhance the mechanical properties of the fibrin network.

Fig. 1. Schema of human hemostasis

Fig. 2. Molecule of fibrinogen. αEC, βC, γC – fibrinogen domains, D and E – fibrinogen fragments, FpA – fibrinopeptide A, FpB – fibrinopeptide B
of the fibrin clot. After the degradation of fibrin stabilized by factor XIII, DD fragments (D-D dimers) are formed (instead of D fragments) [8].

Activation of blood coagulation associated with malignancy

Pathogenesis of the prothrombotic tendency observed in many neoplasms is a consequence of various factors. The inflammatory process induces the stimulation of blood clotting. Furthermore, in both normal and transformed cells, the increased synthesis and release of numerous factors that activate coagulation take place. Tumor progression may also cause the loss of anticoagulant and antiplatelet properties as well as impairing the intravascular fibrinolytic activity [5].

The most important factors responsible for the increased activation of coagulation and the prothrombotic state in malignancy are tissue factor and cancer procoagulant. Tissue factor (TF) is strictly controlled, the main physiological activator of clotting. In tumors, however, there is an increase of its expression as a result of stimulation of its synthesis in both normal and transformed cells in response to proinflammatory factors such as interleukin IL-1β and tumor necrosis factor TNF-α [13]. Tumor cells also produce another strong activator of the coagulation system – cancer procoagulant (CP). Cancer procoagulant may not only activate the coagulation factor X directly, but it is also resistant to the action of physiological anticoagulants (e.g. α1-antitrypsin, α2-macroglobulin and antithrombin III) [14, 15]. The prothrombotic conditions are also enhanced by other procoagulant factors, released from tumor cells, such as a procoagulant homologous to part of HLA-DR (one of the human leukocyte antigens corresponding to the MHC – major histocompatibility complex) and PAA/PCA (platelet aggregating activity/procoagulant activity) – activator of blood platelets and factor X [16, 17]. Moreover, on the surface of malignant cells, the receptors for plasma clotting factor V are expressed and strongly enhance activation of the blood coagulation cascade [18].

Degradation of fibrinogen and fibrin

Dynamic equilibrium between the processes of coagulation and fibrinolysis is crucial for maintaining blood fluidity. The process of blood coagulation leads to the conversion of the soluble plasma protein fibrinogen into insoluble fibrin. The fibrinolytic system is responsible for removal of accumulated fibrin (and fibrinogen) and depends on proteolytic activity of plasmin. The final products of plasmin degradation of fibrinogen are FDPs (fibrinogen degradation products) such as fragment E corresponding to the central E domain and two D fragments corresponding to D domains. In the case of degradation of fibrin stabilized by factor XIII fragment E is formed, but instead of D fragments, D-D dimers are released. Various intermediate products (polypeptides or oligomers) known as XL-DFPs (cross-linking fibrin degradation products) may also appear in the proteolytic degradation of fibrin. Proteolysis of non-stabilized fibrin or fibrinogen starts in the C-terminus of the chain, from which short peptides are removed. Then, after disconnecting a short peptide from the N-terminus of the ββ chain, the molecule of fibrinogen is converted into intermediates X. After asymmetrical cleavage of X, two fragments, D and Y, are created, then fragment Y is cleaved into fragments E and D [19, 20]. In the calcium-free environment fragment D (D1, ‘heavy’ fragment) is further cleaved to a smaller fragment (γγ chain is shortened, ‘light’ D3 fragment is formed). As a result of the loss of part of the γγ chain C-terminus containing polymerization site “a” responsible for interaction with polymerization sites A in the native molecule of fibrinogen, a fragment of D3 has no ability to inhibit polymerization of fibrin monomers [21].

The role of fibrinogen, fibrin and their degradation products in tumor progression and metastasis

Excessive activation of coagulation and extravascular proteolysis is associated with a number of neoplasms. It has been established that this phenomenon is not only a complication of the disease, but also an integral mechanism of tumor growth, vascularization and metastasis. However, the molecular mechanisms of blood clotting proteins (particularly of fibrinogen and its derivatives) and their participation in tumor progression and metastasis remain not fully recognized. Available data confirm the involvement of fibrinogen, fibrin and their degradation products in the pathophysiology of various cancers, mainly by the participation of these proteins in blood clotting, inflammation, angiogenesis and metastasis.

Inflammatory processes and activation of blood coagulation

The pathophysiology of tumors and cancer progression is associated with chronic inflammation, which may be dependent on both a host response to the presence of transformed cells and the effect of numerous secreted cytokines and other inflammatory factors. These factors interfere with the action of the hemostatic system, leading to endothelial dysfunction, platelet activation, stimulation of the coagulation cas-

| Table 1. Pathophysiological action of inflammation (Wang et al. 2005; modified) |
|---|---|
| Mechanisms/proinflammatory factors | Impact on hemostatic system and blood coagulation processes |
| leukocytes | platelet activation |
| | release of neutrophil elastase |
| | secretion of thrombomodulin |
| | by endothelial cells |
| | inactivation of antithrombin |
| proteins of complement system | increase of coagulation factors |
| | increase of tissue factor expression |
| proinflammatory cytokines | stimulation of tissue factor production |
| | decrease of protein S level |
| | increase of adhesive protein expression |
| | platelet activation |
| | increase of PA-1 synthesis |
| chemokines | activation of aggregation and adhesion of platelets |
| | stimulation of leukocyte influx |
cascade and fibrin formation (Table 1) [22]. Malignant cells produce a number of cytokines, e.g. IL-1, IL-6, IL-8, IL-13, TNF-α and transforming growth factor β (TGF-β) [23]. Factors such as IL-1β and TNF-α stimulate endothelium to produce tissue factor (TF). Under physiological conditions, the level of TF is strictly regulated in order to maintain the fluidity of blood, but in cancer its expression increases in normal and neoplastic cells in response to proangiogenic factors [24]. Tissue factor activates the coagulation cascade and induces the formation of thrombin, a mitogenic factor, capable of stimulating tumor growth and metastasis [25]. Both thrombin and fibrin, generated as a result of thrombin action, are proangiogenic factors. Angiogenesis-dependent activation of thrombin may occur by pathways dependent on or independent of the blood coagulation cascade. The mechanism depending on the coagulation cascade is triggered by the activation of coagulation proteins and conversion of zymogen prothrombin into proteolytically active thrombin. Induction of angiogenesis by thrombin in the pathway independent of the blood coagulation cascade takes place with thrombin PARS (protease activated receptors) and G proteins. Thrombin generated in these processes increases the synthesis of many factors, including vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), IL-6, TGF-β, MMP-2 and TF [26].

In vitro studies with cell cultures showed that the production of TF by endothelial cells can also be induced by fibrin in the way of positive feedback (autocrine activation of coagulation) [27]. Fibrin formed as a result of coagulation also affects the inflammatory processes. Research of Laila et al. [28] showed that fibrin influences the expression of IL-8, one of the main factors that induce angiogenesis. Guo et al. [29] described the proinflammatory activities of fibrinogen, fibrin as well as their degradation products. The authors observed that these proteins stimulate expression of CRP in smooth muscle cells from the blood vessel wall. Interleukin 1, TNF-α and TGF-β stimulate endothelial cells to secrete von Willebrand factor, which is in turn involved in platelet adhesion to subendothelial connective tissue, responsible for the loss of endothelial anti-adhesive properties [30]. Interleukin 1, IL-6, TGF-β and TNF-α stimulate the expression of adhesion molecules I-CAM and V-CAM and E-selectin (ELAM-1), proteins participating in the adhesion of cancer cells (including breast and colon cancer and melanoma) to the surface of endothelial cells [31, 32]. Cancer-induced platelet activation is one of the mechanisms of metastasis. The process of platelet adhesion to the surface of tumor cells in blood vessels prevents the identification of transformed cells and their elimination by the immune system [33]. Platelets activated by the pro-angiogenic factor VEGF facilitate the penetration of tumor cells through the vessel wall (extravasation) and metastasis [34].

### Angiogenesis

Since both oxygen and nutrients required for tumor growth may be spread by diffusion only at small distances, this transport mechanism allows the growth of 1–2 mm tumors [35]; the further development of a tumor needs vascularization of malignant tissue. The process of angiogenesis undergoes control of the number of pro- and antiangiogenic factors (Table 2) [36], which may also have effects on various components of the hemostatic system. Even in the early stages of tumor development, the formation of local fibrin deposits and initiation of angiogenesis are observed. One of the initial stages of blood vessel formation in the tumor tissue is the formation of fibrin gel. Fibrin gel is generated as a consequence of the increased transport of fibrinogen and other hemostatic proteins from plasma into the extravascular space and the local activation of coagulation, mainly by TF and CP secreted from tumor cells. Fibrin gel formed around the tumor constitutes a base for migrating macrophages, fibroblasts and endothelial cells. Moreover, the fibrin or fibrinogen degradation products may act as mitogenic factors for endothelial cells [37].

Studies of Bootle-Willbraham et al. [38] on the proangiogenic activity of fibrin degradation products showed the particularly important role of fragment E in this process. It was observed that E fragments stimulated proliferation, migration and differentiation of endothelial cells. In the described experiments, E fragments significantly increased the proangiogenic effect of VEGF and basic fibroblast growth factor (bFGF). Available data indicate that fibrinogen is a potent chemoattractant factor, promoting the migration of endothelial cells [39]. The relationship of fibrinogen and fibrin with angiogenesis in tumors has recently also been confirmed (2010) by results obtained from clinical trials. In those studies, scientists estimated the activity of VEGF, a pro-angiogenic factor affecting the permeability of the blood vessel wall, and the amount of fibrinogen undergoing extravasation in renal cell carcinoma. Higher VEGF activity was accompanied by increasing amounts of fibrinogen (and fibrin) accumulated outside the blood vessel [40]. Angiopoietins, together with VEGF, participate in the development of vascularization. There

| Pro-angiogenic factors | VEGF – vascular endothelial growth factor |
|------------------------|-----------------------------------------|
|                        | bFGF – basic fibroblast growth factor    |
|                        | IGF-1 – insulin-like growth factor       |
|                        | TGF-α – transforming growth factor α     |
|                        | TGF-β – transforming growth factor β     |
|                        | TNF-α – tumor necrosis factor α          |
|                        | PDGF – platelet-derived growth factor    |
|                        | HGF – hepatocyte growth factor           |
|                        | GMCSF – granulocyte macrophage colony-stimulating factor |
|                        | IL-6 – interleukin 6                     |
|                        | Integrins α, β, α, βs                    |
|                        | MMPs – matrix metalloproteinases         |
|                        | ANGPT-1 – angiopoietin 1                 |

| Anti-angiogenic factors | PF-4 – platelet factor 4 |
|------------------------|--------------------------|
|                        | TSP-1 – thrombospondin 1 |
|                        | Angiostatin (38 kDa part of plasmin) |
|                        | TIMP-1, -2, -3 – tissue inhibitors of matrix metalloproteinases |
|                        | INF-α – interferon α     |
|                        | IL-1 – interleukin 1     |
|                        | Endostatin (20-kDa C-terminal fragment of type XVIII collagen) |
|                        | ANGPT-2 – angiopoietin 2 |
are three types of these proteins: Ang-1, Ang-2, Ang-3. It is known that the angiopoietins and their receptor Tie-2 play an important role in formation and maintenance of the vascular wall, including tumor angiogenesis. So far, the best known are Ang-1 and Ang-2, which are ligands for receptor tyrosine kinase (Tie-2), specific for endothelial cells of blood vessels. Biochemically, angiopoietins are proteins in which beyond the N-terminal helical segment also a C-terminal fragment, homologous to the C-ends of fibrinogen \( \alpha \), \( \beta \) and \( \gamma \) chains, is located. Ang-1 binds to Tie-2, and then activates this receptor by the induction of autophosphorylation of tyrosine residues, thereby participating in the development of endothelium of newly formed vessels. The interaction of Ang-1 with the receptor Tie-2 triggers the conversion of primitive vessels as well as maintaining and stabilizing mature vessels by promoting interactions between endothelial cells and extracellular matrix. Since Ang-1 mediates the maturation of blood vessels, this activity may have therapeutic significance in the specific inhibition of tumor vascularization [41]. Ang-2 is an antagonist of Ang-1 and binds to the same receptor (Tie-2) that prevents the formation of blood vessels. Ang-2, in the absence of VEGF, can induce apoptosis of endothelial cells and diminish tissue vascularization. In the presence of VEGF, Ang-2 may facilitate the migration and proliferation of endothelial cells [42]. Due to the roles of both groups of proteins in vascularization of malignant tissue, the relationship and function of the C-terminal domains of angiopoietins and fibrinogen seem to be particularly interesting. Similar C-terminal domains in proteins such as tenasin, fibroleukin and ficolin are also present; moreover, it is known that these proteins may be involved in development of various tumors [43–45].

Metastasis

The constitutive synthesis of fibrinogen takes place mainly in the liver, but about 5–10% of the pool of this protein is formed in the megakaryocytes. Since fibrinogen is an acute phase protein, in response to inflammatory agents its concentration is increased up to 2–10-fold. It is believed that inflammation, associated with cancer, is primarily responsible for the increased level of plasma fibrinogen. However, studies by Rybarczyk and Simpson-Haidaris [46] on breast cancer showed that the tumor tissue can also be the source of fibrinogen. The authors suggest that the presence of fibrinogen within the tumor is probably one of the factors necessary for its growth and metastasis [46]. The participation of fibrinogen in the processes associated with tumor formation and metastasis is still only partly understood. Research on the development of tumors in transgenic animals with a lack of fibrinogen, performed by Palumbo et al., showed that fibrinogen is not necessary for the vascularization and growth of primary tumors, but they confirmed that the protein is very important in the process of metastasis [47]. It has also been suggested that fibrinogen may be a critical factor in determination of the metastatic potential of transformed cells in lung cancer and melanoma [48]. However, clinical studies indicate that an elevated level of fibrinogen (hyperfibrinogenemia) correlates with the stage of metastasis and poor prognosis in patients with gastric cancer. A correlation between increased plasma fibrinogen and progression of cancer was also found in patients with colorectal cancer [49]. Increased concentration of fibrinogen is also correlated with the progression of tumor metastasis and weak response to the application of chemotherapy in patients suffering from esophageal cancer [50]. Results from clinical studies suggest that an increased level of fibrinogen may be an independent predictive marker in cervical cancer [51]. In patients with different types of cancer the concentration of fibrinopeptide A varies depending on the stage of tumor growth or regression of lesions. The presence of stabilized fibrin (cross-linked fibrin, XLF) was found in the endothelium of newly formed blood vessels in invasive types of cancer, but was not detected in the vessels of benign tumors [52]. Nevertheless, the studies by Biggerstaff et al. demonstrated that soluble fibrin might be involved in metastasis. Since the interaction of platelets with tumor cells is an important mechanism in the formation of metastases, the authors studied the effect of fibrin monomers on the adhesion of platelets to transformed cells. The cited experiments showed that the presence of fibrin greatly enhances the adhesion of transformed cells, increasing the dissemination of lung cancer cells by about 65% compared to cells not incubated with fibrin [53]. The presence of soluble fibrin in plasma of patients with malignant neoplasms may be a marker of the hypercoagulative state and disseminated intravascular coagulation (DIC). There are also data indicating the immunosuppressive properties of non-stabilized fibrin. Non-stabilized fibrin inhibits the adhesion and cytotoxicity of lymphocytes and LAK cells (interleukin-2-activated lymphocyte), and thus may significantly reduce the effectiveness of transformed cells’ elimination by the immune system [54].

The presence of D-dimers in plasma is a known marker of stabilized fibrin formation, indicating the increased activity of coagulation and fibrinolysis. Determination of the DD level is one of the widely used diagnostic parameters, useful in the detection of thromboembolic complications. An elevated level of DD is used inter alia in the diagnosis of deep vein thrombosis and pulmonary embolism [55]. The concentration of D-dimers may also be one of the markers of cancer progression. Its elevated level is observed in patients with various malignant tumors, including breast, lung, colorectal and ovarian cancers. It was confirmed that the level of DD in breast cancer correlates with the progression of the disease and the amount of metastases [56–58]. This relationship may be dependent on the increased fibrinolytic activity in the process of metastasis, although the immediate effect of D-dimers also cannot be excluded. Clinical trials involving patients with esophageal cancer also showed that the increase of D-dimers is significantly correlated with the number of metastases in lymph nodes. These results indicate that the determination of concentrations of these fibrin fragments provides important information on the progress of the lesions and lymph nodes and may be part of the diagnosis prior to surgery [59]. On the other hand, it has been shown that domain \( \gamma C \) of fibrinogen, a part of fragment D, inhibits tumor growth, proliferation of capillaries and metastasis in breast cancer model Met-1 in vitro [60], which indicates that the function of fibrinogen degradation fragments in metastasis may be very complex.
The role of hemostatic factors, particularly fibrinogen, fibrin and products of their degradation, in the progression of various tumors is not yet sufficiently known. The final effect in the progression of cancer may be imposed by the action of many different, often antagonistic factors that are involved in blood clotting. Particular attention should be paid to the participation of fibrinogen in neoplasia and on the similarity within its C-terminal sequence as well as angiopeptins – proteins involved in blood vessel formation, and thus also in the progression of cancer. Other proteins, such as tenascins, fibroleukin and ficolins, containing a C-terminal domain homologous to fibrinogen C-termini, may be involved in cancer development. Many of these proteins might be potential markers in the diagnosis of cancer. Better understanding of the role of hemostatic factors, particularly including fibrinogen together with other non-hemostatic proteins related to it, may also allow new cancer therapies to be developed.

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