Abstract. Accumulating evidence has revealed the role of various components of the coagulatory system in different stages of carcinogenesis including precancerous and initial stages, tumor growth, angiogenesis, stroma generation, and metastasis of malignant cells. This comprehensive review discusses major points of evidence, in addition to recent findings on specific factors associated with the paradigm of oral squamous cell carcinoma. During carcinogenesis, angiogenesis is favored by local conditions of hypoxia, cell-to-cell interactions, and by expression of paracrine growth factors and inflammatory cytokines. In the oral region specifically, genetic association studies have revealed that constitutively high gene expression of certain inflammatory cytokines plays a major role in carcinogenesis. Tissue factor (TF) has a physiological role in hemostasis, but it also constitutes a notable procoagulant in many types of cancer, since it appears to be constitutively expressed by tumor cells. Furthermore, its pathway regulates mechanisms which involve plasmin and matrix metallo-proteinases, both of which seem to be critical in oral carcinogenesis. Thrombin has a central role in hemostasis but it may also promote angiogenesis through pathways independently of fibrin generation. Thrombomodulin may act through attenuation of the tumor-promoting properties of thrombin, but it also may function as a cell-to-cell adhesion molecule, independently of its anticoagulant action. The activation of fibrinogen by thrombin and its cleavage to fibrin monomers result in the rapid formation of fibrin matrix. Furthermore, it is well documented that fibrinogen and cross-linked fibrin reside inside the tumor stroma, facilitating its remodeling, angiogenesis, tumor growth and metastasis. In conclusion, the hemostatic system contributes to the development of the malignant phenotype acting on many different levels.

A bleeding diathesis and a systemic activation of the coagulation cascade contribute considerably to the morbidity and mortality of cancer patients (1-2). In some instances, the disruption of hemostatic mechanisms, such as venous thromboembolism, may even precede the clinical manifestations of malignancy (3). However, it is well established that the activation of coagulation is not merely an epiphenomenon of cancer (4-6).

The present review discusses the role of various components of the clotting system in different stages of carcinogenesis, including precancerous and initial stages, tumor growth, angiogenesis, stroma generation, and metastasis of malignant cells. Furthermore, specific findings of recent genetic studies involving functional gene polymorphisms of clotting system components, associated with the well studied paradigm of oral squamous cell carcinoma are presented.

Coagulatory System and Platelets

Coagulation is a complex enzyme cascade by which fibrin is produced forming the basis of a clot. Cancer-related thrombosis represents a complex imbalance of coagulation and fibrinolysis, which also involves formation and degradation of extracellular matrix (ECM) (Figure 1). As new vessels within a tumor leak fibrin into the extravascular space, they persistently activate the coagulatory system, both locally and systemically, producing the clinical appearance of a wound that does not heal (7).
The most essential components of the coagulation and fibrinolysis systems are associated with the endothelial cell membrane, including tissue factor (TF), thrombin and urokinase receptors. They become exposed when vessels are injured and platelets bound to them at early stages of either coagulation or inflammation. Consequently, platelets release vascular endothelial growth factor (VEGF) and other growth factors into the circulation, thus attracting inflammatory cells to the site of injury (7). VEGF is known to promote both vascularization and tumor growth. On the other hand, in an effort to regulate the extent of tissue repair, platelets also contain hemostatic factors that inhibit angiogenesis, such as plasminogen activator inhibitor-1 (PAI-1) (7).

Figure 1. Pathogenesis of the prothrombotic state in cancer patients (adapted from (1) with modifications). The central role of the tumor cell is illustrated, since: a) It directly interacts with platelets (P) inducing their aggregation; b) it interacts with vascular endothelial cells through several cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), which induce the expression of tissue factor (TF) by the endothelial cells, as well as the release of von Willebrand’s factor (vWF), of leukocyte adhesion molecules, of platelet activating factor (PAF) and of plasminogen activator inhibitor type-1 (PAI-1), while at the same time down-regulating the expression of thrombomodulin, protein C (PC) receptor and tissue plasminogen activator (tPA); c) it stimulates leukocytes to produce TF and cytokines (TNF-α, IL-6); d) it directs the expression of procoagulants of TF, of cancer procoagulant (CP), of factor V receptor (FVr) and of mucin. The levels of IL-6, TNF-α, PAI-1 and VEGF (shown in bold) have been associated with carcinogenesis in the oral region by genetic association studies (12, 13, 42, 43).

Angiogenesis

The generation of new vessels from pre-existing vasculature is an essential step for tumor survival, invariably observed in cancer pathology (8). Angiogenesis seems to be well controlled during embryogenesis, the menstrual cycle, wound healing, and inflammation, and a balance is eventually established between the various inhibitors and promoters of angiogenesis. In neoplasia, as the tumor develops, a pro-angiogenic environment is favored by local conditions of hypoxia, cell–to–cell interactions, expression of paracrine growth factors and of inflammatory cytokines (9). This progressive nature of the tumor differs from the process of wound healing (10, 11).
Hemostatic mechanisms may directly or indirectly influence angiogenesis through different pathways involving the release of proangiogenic and antiangiogenic factors from activated platelets and tumor cells, thus promoting the formation of a fibrin-rich provisional ECM and thrombin signaling via activation of G-protein-coupled protease activated receptors on the endothelial cell surface (12). The interaction of angiogenesis-related factors, such as tumor necrosis factor-alpha (TNF-α) with interleukins (IL) 6 and 8, as well as their accumulated contribution to neoplasia have been reported for oral cancer (13, 14). Functional DNA polymorphisms affecting gene expression and the serum or the saliva levels of cytokines IL-6, IL-8, and TNF-α have been associated with increased risk for the development of oral squamous cell carcinoma (13, 14). There seems to be a genetic predisposition for oral neoplasia in certain individuals who have genotypes which result in high constitutive production of specific cytokines (13). According to these preliminary findings, such individuals may have 3-15 times higher risk of developing oral cancer than the general population (13).

Tissue Factor

From the perspective of in vitro testing, the coagulatory cascade is artificially divided in the intrinsic or contact pathway and the extrinsic or tissue factor (TF) pathway (Figure 1). There is a cross-talk between the two pathways because both TF and thrombin can activate factor IX (FIX) (15). As the physiological initiator of coagulation, TF is constitutively expressed on subendothelial fibroblasts and smooth muscle cells that are only exposed to blood upon vascular damage. TF is also expressed on peripheral blood monocytes and on vascular endothelia after exposure to activating or inflammatory stimuli such as endotoxin.

Structurally, TF is a transmembrane glycoprotein which belongs to the class 2 cytokine-receptor superfamily (16). It has a 219-amino acid extracellular ligand-binding domain which interacts with FVII/FVIIa, a 29-amino acid hydrophobic transmembrane region and a 21-amino acid intracellular tail (16). When plasma comes in contact with cells in extravascular sites that express TF, a complex is formed on the cell surface with the circulating FVII, which is further activated to FVIIa by limited proteolysis. About 1% of FVII is already activated in circulation and can also bind directly to TF with high affinity (17). These initial TF/FVIIa complexes are used for the downstream activation of proteases that will subsequently activate the bound FVII, forming a positive feedback loop.

Beyond its physiological role in hemostasis, TF appears to have important functions both in normal embryonic and tumor angiogenesis. The former has been demonstrated by the fact that TF-null mice die from abnormal circulation and defective blood vessel development inside the yolk sac (18). Similarly impaired vascular formation and death was observed in heterozygous VEGF-deficient embryos, pointing to the interplay between TF and VEGF (19). These non-hemostatic effects seem to be mediated through clotting-dependent and -independent intracellular signaling pathways that change the transcription rate of proangiogenic factors, especially of VEGF. In the clotting-dependent pathways TF, interacts with FVIIa, producing FXa and thrombin (Figure 1).

The secondary messengers involved in different cell types, are intracellular calcium oscillations, activation of several mitogen-activating protein (MAP) kinases, transcription of genes such as EGR1 (early growth response protein 1) and activation of protease-activated receptors (PARs) (20). The latter are a novel family of seven transmembrane-spanning G-protein-coupled receptors up-regulated in various types of cancer cells, including those of breast, prostate, colon and melanoma (21, 22). It is well documented that TF-FVIIa induces cell signaling via direct activation of PAR-2 that is independent of thrombin generation and that the ternary complex of TF-FVIIa-FXa is more efficient than the binary complex, and activates both PAR-1 and PAR-2 (23, 24). The TF cytoplasmic domain may exert a negative regulatory control over PAR-2 signaling. Genetic deletion of the TF cytoplasmic domain in mice results in accelerated PAR-2-dependent angiogenesis in synergy with the platelet-derived growth factor (PDGF) but not with VEGF (25). In this context, cancer cells expressing TF are likely to progressively regulate (through distinct mechanisms) angiogenesis, primary tumor growth and metastasis via autocrine signaling (24, 26). In the coagulation-independent mechanisms, TF directly up-regulates the expression of the proangiogenic factor VEGF and possibly other growth factors, whereas it diminishes the expression of the antiangiogenic peptide thrombospondin (27). In this case, the increased expression of VEGF is regulated via the cytoplasmic tail of TF, with the use of protein kinase C (28) and is independent of the TF ligand-binding extracellular domain, as shown in some melanoma cell lines (29).

Since TF is expressed constitutively by tumor cells, in contrast to normal tissues, it constitutes a notable procoagulant in many types of cancer, including breast cancer (30), non-small lung cell carcinoma (31), head and neck squamous cell carcinoma (32, 33), prostate carcinoma (34), malignant glioma (35), colon adenocarcinoma (36), and pancreatic cancer (37). Other tumor types induce the expression of TF in host macrophages and endothelia (20). The increased expression of TF appears to be the result of oncogenic events occurring in cancer cells, caused by mutant oncogenes K-RAS, EGFR (epidermal growth factor receptor), PML-RARA (promyelocytic leukemia-retinoic acid receptor alpha), as well as by the inactivation of the tumor suppressor genes p53 or PTEN (38). In addition, high levels of TF (30), and VEGF (39) seem to be associated with advanced cancer.
and poor prognosis (36). TF aids in angiogenesis though induction of VEGF (40) and possibly in tumor invasion and metastasis by up-regulating the secretion of urokinase plasminogen activator receptor (uPAR) (41).

Interestingly, both VEGF and PAI-1 levels have been associated with carcinogenesis in the oral region (42, 43). An association of functional DNA polymorphisms affecting the gene expression of VEGF and PAI-1 with increased risk for oral cancer has been found (42, 43). A genetic predisposition for development of early stages of oral neoplasia was detected in certain individuals with a genotype resulting in low production of VEGF (44). Those findings, in addition to the known limited tumor-associated neo-angiogenesis in the oral mucosa because of its rich vasculature, may indicate that the underlying neoplasia mechanism might not involve angiogenesis but other VEGF-related functions such as thrombosis. On the other hand, individuals with a higher expressing genotype in the promoter region of the \textit{PAI-1} gene have a higher risk of developing early stages of oral cancer (43). Possibly, increased levels of PAI-1 promote initial development of oral cancer through regulation of cell detachment by decreasing cellular adhesion. Yet, they seem to have a protective role against later stages of malignancy by interfering with the proteolytic activity of matrix metalloproteinases (MMPs), which remodel the tissue by degrading the major components of the extracellular proteins, including the type I collagen (43).

There is interplay between TF and VEGF, one promoting the production of the other. Both are stimulated by hypoxia but different pathways are involved. VEGF can trigger TF in endothelia (through EGR1, distinct from inflammatory stimuli) (44), TF can also trigger the expression of VEGF in various cells of tumor stroma and parenchyma, thereby creating a vicious cycle (20). This close relationship is further indicated by the co-localization of TF and VEGF in various types of human cancer which correlates with microvascular density (36, 45). Finally, recent reports underline the critical role that tumor cell-associated TF may have in metastatic spread, along with other hemostatic components (46, 47). Through a fibrinogen- and-platelet dependent evasion of natural killer cell-mediated clearance of tumor cells, TF was linked with increased survival of micrometastases in the lung (47).

The interplay of angiogenesis and hemostasis may impact progression of cancer locally and systemically. The more knowledge is accumulated to clarify these concepts the better potential therapeutic management may be effected by combining surgery, radiation, chemotherapy, and anti-angiogenic agents.

**TF Pathway Inhibitor**

Another protease inhibitor constitutively released from endothelia is TF pathway inhibitor (TFPI). TFPI inhibits circulating FXa but mainly acts to down-regulate TF-induced tenase complex (complex of Ca$^{2+}$ and factors VIIIa, IXa and X). This task is accomplished through binding of the TFPI/FXa complex to the TF/FVIIa complex and by inactivating the latter through this quaternary complex formation, thereby by shutting down the TF-induced tenase pathway (48). Both circulating rTFPI and tumor cell-associated TFPI reportedly reduced the experimental lung metastasis of B16 murine melanoma by approximately 80% (49).

A second TF inhibitor, TFPI-2, which has similar overall domain organization and considerable primary amino acid sequence homology to TFPI (50), is an emerging protease inhibitor that seems to have an important role in normal ECM remodeling. Human TFPI-2 is synthesized by endothelia, fibroblasts and smooth muscle cells of the vasculature and is then located in the subenthothelial ECM compartment. It directly inhibits plasmin and indirectly MMPs by inactivating serine proteases that convert proMMPs to their active form (51). In this regard, TFPI-2 may reduce the invasive potential of tumors. In the well studied paradigm of oral cancer, several MMPs have been associated with tumor advancement (including MMP-1, -3, -7, -9 and -13) (52-56). In all cases, functional polymorphisms in the promoter region of the \textit{MMP} genes, affecting their expression, seem to increase predisposition of developing oral cancer in certain individuals (52-56).

The expression of TFPI-2 diminishes with the increasing degree of malignancy, as was demonstrated through immunohistochemical localization in a series of human tumors (57). In addition to being anti-invasive, TFPI-2 has antiangiogenic properties because an anti-TFPI-2 IgG results in detachment of endothelia from the ECM (58). It also exhibits pro-apoptotic properties (59) and was recently recognized as a tumor-suppressor gene since its silencing is involved in melanoma metastasis (60).

**Thrombin**

Thrombin has a central role in hemostasis as it is the most effective agonist for platelet activation and activates various zymogens and co-factors culminating in the formation of the fibrin clot. Thrombin acts on fibrinogen, factors XIII, V and VIII, platelet membrane GPV, protein S and C (61). It is generated by many different types of tumor cells suggesting additional tumor-promoting properties at different levels (11, 12, 62). Like TF, thrombin may promote angiogenesis through different ways, and independently of fibrin generation.

Thrombin facilitates the detachment of endothelia by preventing their adhesion to collagen IV and to laminin (63). It also activates gelatinase A (MMP-2), which degrades collagen IV and releases tissue plasminogen (t-PA) and PAI-1, further enhancing the migratory potential of endothelia through basement membranes (64). Additional important pro-angiogenic properties that thrombin exhibits...
on vascular cells, mediated through PARs, is the increased expression of VEGF from platelets and tumor cells, and the up-regulation of VEGF receptors on endothelial cells (63-65). The latter effect results in potentiation of the action of VEGF, which is a specific endothelial cell mitogen and a key angiogenic factor (66).

Moreover, thrombin increases the expression of αvβ3 integrin and may serve as an additional ligand for it. Integrin αvβ3 is considered a marker of the angiogenic phenotype of endothelial cells in tumor vessels and interacts with ECM proteins, including fibrinogen, fibronectin, vitronectin, osteopontin and thrombospondin. The binding to αvβ3 promotes cell attachment, migration, proliferation and prevents apoptosis (67, 68). Endothelial cells cultured on plates coated with thrombin had a lower level of apoptosis, suggesting a thrombin-induced αvβ3-dependent endothelial cell survival (67, 68). Several thrombin-related factors have already been associated with oral carcinogenesis (42, 43, 69-71).

Besides endothelial cells, thrombin has diverse actions on platelets, tumor cells and inflammatory cells that result in tumor progression. It activates platelets, leading to the aggregation and release of their granules which possess numerous pro- and anti-angiogenic factors. Thrombin is a potent mitogen inducing the proliferation of smooth muscle cells as well as this of tumor cells, while it increases their adhesiveness favoring the formation of tumor-platelet aggregates, migration and metastasis (24, 72). The multifunctional role of this protease is further demonstrated by the fact that it has antiangiogenic properties. Prothrombin kringel 2 domain as well as two prothrombin fragments (F1 and F2) generated during activation of thrombin, inhibit angiogenesis (73, 74).

Finally, thrombin inhibits clot lysis and modulates fibrinolysis through activation of thrombin activatable fibrinolysis inhibitor (TAFI), but the role of this factor in malignancy is poorly understood. TAFI cleaves C-terminal lysine residues from fibrin, thereby preventing plasminogen, plasmin and t-PA from binding to fibrin (75). High TAFI antigen levels have been reported in lung cancer patients (76), while reduced TAFI activity, but not TAFI antigen, have been documented in patients with acute promyelocytic leukemia (77). Deficiency of TAFI in mice injected with different cancer lines did not affect the primary tumor growth, the tumor architecture or the invasive potential (78). In regard to neovascularization, TAFI reduced the formation of capillary-like tubular structures in vitro, in human microvascular endothelial cells possibly via a thrombin-independent pathway (79).

Interestingly, while prothrombin has not been found to be associated with risk for oral squamous cell carcinoma, increased TAFI activity seems to inhibit tumor progression by reducing plasminogen activation (42, 69, 71). A genetic association study showed that a DNA polymorphism affecting the high activity of TAFI was significantly reduced in patients with oral cancer compared to controls (71). The prophylactic effect of the increased TAFI activity might result from reduction of plasmin and inhibition of extracellular matrix dissolution.

**Antithrombin**

After cleavage from thrombin, antithrombin undergoes a change in its structural conformation, which lacks anticoagulant but exhibits antiangiogenic activity and antitumor growth properties. The antiangiogenic antithrombin exerts its effects through down-regulation of the proangiogenic heparin sulfate proteoglycan in endothelial cells (80), and may globally alter gene expression in endothelium, possibly through a putative endothelial cell ligand-receptor signaling mechanism (81). Therefore, it is a potent inhibitor of VEGF and beta fibroblast growth factor (bFGF)-induced endothelial cells proliferation and angiogenesis (82). A prelatent conformation of antithrombin, obtained by heat treatment, which has undergone only limited conformational change and is still able to bind heparin and inhibit thrombin, also exhibits potent antiangiogenic and tumor inhibitory activities (83).

Recently, it has been postulated that the binding of heparin to the antiangiogenic cleaved or latent forms of antithrombin is crucial for the expression of its antiangiogenic activity (84). However, in oral cancer in particular, antithrombin may not have any significant antitumor growth properties. This might be due to the fact that the oral region has a rich vasculature and that low VEGF levels (instead of high ones) are strongly associated with oral carcinogenesis (43).

**Thrombomodulin**

Thrombomodulin is an endothelial cell surface-associated protein that forms a complex with thrombin leading to activation of protein C (Figure 1). Activated protein C cleaves non-platelet-associated FVa and FVIIa, thereby inactivating the respective tenase and prothrombinase complexes, thus down-regulating thrombin formation. In addition to this anticoagulant effect, thrombomodulin reduces fibrinolysis by activating TAFI in plasma (85).

The role of thrombomodulin in cancer biology seems to be multifaceted. A correlation between reduced thrombomodulin expression and shorter survival or increased metastasis in a variety of human tumors has been demonstrated (86, 87) and it has been shown that in vitro thrombomodulin reduces tumor cell proliferation and invasion (88, 89). The synthesis of thrombomodulin and protein C is increased by VEGF, while many inflammatory cytokines, such as IL-1 and TGF-β, down-regulate thrombomodulin (90). Therefore, thrombomodulin may act through attenuation of the tumor-
promoting properties of thrombin. Independently of its natural anticoagulant action however, thrombomodulin can function as a cell–to–cell adhesion molecule through a Ca\(^{2+}\)-dependent interaction of its lectin-like domain, which restrains tumor growth in vivo (91). There are reports suggesting that thrombomodulin is an alternative useful clinical predictor of tumor prognosis (87, 92), however, no genetic association of functional polymorphisms affecting the activity of thrombomodulin, of FV or of IL-1 with oral carcinogenesis has been detected (69, 93, 94).

**Fibrinogen and Cross-linked Fibrin**

After activation by thrombin, fibrinogen is cleaved to fibrin monomers that are rapidly combined to form a fibrin matrix. Thrombin also activates FXIII that converts the soluble fibrin into an insoluble fibrin polymer. In addition, by linking α2-antiplasmin inhibitor to fibrin activated FXIII protects the clot against fibrinolysis (95).

Besides the critical role of fibrinogen in hemostasis, this protein is also important in tumor biology. It is well documented that fibrinogen and the cross-linked fibrin reside inside the tumor stroma. This deposition is indicative of the extravascular activation of the hemostatic mechanism, a process favored by the increased vascular permeability of the newly formed tumor vessels (8). The fibrin gel provides a provisional matrix, enriched in growth factors, that promotes angiogenesis and cancer cell growth, as well as provides a surface for the prothrombinase assembly, a function normally carried out by platelets in intravascular clotting. Various growth factors, such as VEGF, bFGF and insulin-like growth factor-1 (IGF-1), are sequestered and protected from degradation in fibrin (20), and some tumor cells are capable of controlling their own microenvironment by endogenously synthesizing and secreting fibrinogen (96).

In addition, fibrin can induce the expression of the proangiogenic IL-8 in vitro, in oral and pharyngeal tumor cells but not in a non-tumorigenic oral cell line, which points to the specificity of fibrin in eliciting this response (97). Furthermore, fibrin matrices support endothelial adhesion and promote the migration and survival of various types of cells, including transformed cells, macrophages and fibroblasts (98). Interestingly, genetic association studies indicate that the thinner the fibrin polymer made by FXIII, the higher the risk of initiation of oral carcinogenesis, while increased levels of IL-8 also promote formation of oral squamous cell carcinoma (70, 99).

Cells interact with fibrin via integrin binding sites located at the amino acids 95-98 (RGDF) and 572-575 (RGDS) of human the fibrinogen (100), while other proteins found inside fibrin, such as fibronectin, also offer additional binding sites (8). Non-integrin binding sites of fibrinogen, such as the N-terminal β15-42 sequence, bind to vascular endothelial (VE)-cadherin (101), on the endothelial surface and possibly trigger vascular development (102). The latter interaction may account for the increased angiogenesis and tumor growth observed in mice lacking β3 or both β3 and β5 integrins (103).

Fibrin mesh is further implicated in metastasis. Aggregates of tumor cells and platelets are rich in fibrin, enhancing further platelet adhesion to circulating tumor cells and endothelial cells, thereby, facilitating metastasis (104). Fibrin and fibrinogen, however, do not appear to play a critical role in the growth of established metastases as demonstrated in studies of fibrinogen-deficient mice (105, 106). In lung carcinoma and melanoma cell lines, fibrinogen deficiency strongly diminished, but did not prevent, the development of lung metastases, while angiogenesis and tumor stroma formation was equivalent both in normal controls and in deficient mice (105). These results indicate that fibrin deposition may not be essential for the tumor establishment and show how complex the interactions between the various components of the ECM and the tumor cells are, during tumor growth and invasion. In addition, fibrin, along with platelets, shelters tumor cells from the host’s antitumor cell immune surveillance mechanisms (46).

**Fibrinolysis**

The aforementioned provisional matrix finally undergoes remodeling and is transformed into mature connective tissue stroma, which resembles the stroma of healing wounds in its constituent elements (8, 10). In fact, the deposition of fibrin gel in tumors is balanced between deposition from clotting activation and dissolution through activation of the fibrinolytic pathways (8). Angiogenesis involves a sequence of key events that include focal detachment of endothelial cells from the basement membrane, localized proteolytic degradation of the basement membrane and ECM invasion, leading to capillary tube formation and vascular remodeling (107).

A breach of the basement membrane is the critical initial step in tumor invasion. Malignant cells along with stromal cells secrete a variety of proteases that degrade one or more components of the basement membrane. Such enzymes are the urokinase-type plasminogen activator (uPA) and the MMPs (108). Fibrinolytic activity depends on the balance between plasminogen activators, such as tPA and uPA, and their inhibitors, such as PAI-1 and α2-antiplasmin. In addition, the contact system activators, kallikrein, high-molecular-weight kininogen and FXIIa convert plasminogen to plasmin. Among plasminogen activators the one strongly associated with tumor progression is uPA. Among the above mentioned factors, genetic association studies have shown that PAI-1 is strongly associated with initial stages of oral carcinogenesis, while FXII seems to plays no role in mouth tumors (42, 70).
The Hemostatic System as a Target for Anticancer Therapy

The hemostatic system contributes to the development of the malignant phenotype acting on many different levels (Figure 1). Common events in cancer biology, namely the activation of oncogenes, the inactivation of tumor suppressor genes and changes in tumor microenvironment, such as hypoxia, exposure to cytokines and altered cellular adhesion, culminate in the induction of TF, uPAR, PAI-1 and PARs (38). The result is complex interactions affecting aggressive local growth, cellular migration, invasion, angiogenesis, metastasis and tumor coagulopathy.

The relationship between hemostasis and carcinogenesis may be exploited therapeutically. Several drugs affecting the coagulation process may have promising anticancer activity, including heparin, aspirin, warfarin, angiostatin, endostatin and non-steroidal anti-inflammatory substances.

In conclusion, accumulating evidence over the past two decades has illuminated the important role of various components of the coagulatory system in different stages of carcinogenesis. Based on the paradigm of oral cancer, there seems to be an emerging notion of genetic predisposition towards the development of the malignant phenotype in some individuals, whose genetically-determined level of constitutive gene expression leads to biologically important levels of certain factors associated with both hemostasis and tumor progression, such as cytokines IL-6 and TNF-α.

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