Crosstalk between cancer and haemostasis
Implications for cancer biology and cancer-associated thrombosis with focus on tissue factor

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Cancer, thrombosis, tissue factor, microparticles

Summary
Cancer is characterized by bidirectional interrelations between tumour progression, coagulation activation, and inflammation. Tissue factor (TF), the principal initiator of the coagulation protease cascade, is centrally positioned in this complex triangular network due to its pleiotropic effects in haemostasis, angiogenesis, and haematogenous metastasis. While formation of macroscopic thrombi is the correlate of cancer-associated venous thromboembolism (VTE), a major healthcare burden in clinical haematology and oncology, microvascular thrombosis appears to be critically important to blood-borne tumour cell dissemination. In this regard, expression of TF in malignant tissues as well as shedding of TF-bearing microparticles into the circulation are thought to be regulated by defined genetic events relevant to pathological cancer progression, thus directly linking Trousseau’s syndrome to molecular tumourigenesis. Because pharmacological inhibition of the TF pathway in selective tumour types and patient subgroups would be in line with the modern concept of individualized, targeted anti-cancer therapy, this review will focus on the role of TF in tumour biology and cancer-associated VTE.

In patients with cancer, there are bidirectional interrelations between tumour biology, coagulation activation, and inflammation (Fig. 1). For instance, local or systemic activation of the coagulation protease cascade may directly influence cellular properties relevant to cancer progression, including tumour cell adhesion, migration, and invasion (1).

In particular, formation of new blood vessels (i.e. tumour angiogenesis) and haematogenous metastasis appear to be critically dependent on various components of the activated haemostatic and fibrinolytic systems (1–3).

While, in a subgroup of cancer patients, activation of the coagulation protease cascade may become clinically apparent as venous or arterial thromboembolism or decompensated disseminated intravascular coagulation (DIC), almost all patients with advanced tumours show laboratory evidence of low-grade systemic coagulation activation, as indicated, for example, by elevated plasma D-dimer (4, 5). In this regard it is noteworthy that several studies have linked enhanced intravascular coagulation activation to adverse clinical outcomes in patients with various types of malignancies (6–9).

However, haemostatic components not only drive tumour progression, but also promote inflammation on various levels. For instance, activated coagulation factors VIIa and Xa as well as thrombin may modulate cellular gene expression through signaling via protease-activated receptors (PARs), resulting in the up-regulation of proinflammatory cytokines such as interleukin-6 (IL-6), IL-8, and IL-10 (10–13). Furthermore, there is intensive crosstalk between the coagulation and complement

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Zusammenfassung
Da eine pharmakologische TF-Hemmung in selektierten Patientensubgruppen dem modernen Konzept einer individualisierten, zielgerichteten Krebsterapie gerecht werde, befasst sich diese Arbeit mit der Rolle von TF in der Tumorbioiogie und der tumorassozierten VTE.
Central position of tissue factor (TF) in the triangular network characteristic of malignant disease (Fig. 1). Because this appears to be true for asymptomatic VTE (e.g., detected on diagnostic or restaging imaging procedures) (24). The clinical observation that cancer-associated VTE is associated with an unacceptable high recurrence rate during treatment with vitamin K antagonists underscores the intensity of the hypercoagulable state observed in most malignancies (25).

While Trousseau’s observations focused on the clinical link between cancer and thrombosis, it was probably the German surgeon Theodor Billroth who first microscopically identified tumour cells in a cancer patient’s blood clot, hypothesizing that coagulation activation was required for efficient haematogenous metastasis (26). In fact, it has become clear from both earlier and more recent animal studies that formation of a fibrin(ogen) thrombus around circulating tumour cells is a critical step during the blood-borne phase of the metastatic cascade (1, 27). Although direct in-vivo evidence for this hypothesis in cancer patients is still lacking, microscopic tumour emboli resembling a thrombotic microangiopathy may be detected on autopsy in patients with gastric or ovarian carcinomas (28–31). Interestingly, immunohistochemistry in some of these patients revealed strong TF staining on tumour cells, suggesting that the expression of procoagulant activity was an important determinant for tumour cell embolization.

In summary, while formation of macroscopic thrombi is the pathological correlate of cancer-associated VTE, experimental and circumstantial clinical evidence suggests that formation of microthrombi is critical to haematogenous metastasis. In this regard, TF has been implicated in both cancer-associated VTE and tumour cell-induced microvascular thrombosis.

TF in primary tumours

Tumour cell TF and cancer biology

Independent studies suggest that tumourigenesis and cancer progression are associated with enhanced TF expression (32–37). In primary tumours, TF may be produced by both cancer cells and cells of the tumour

cascades (14), and activated platelets enhance inflammation through the expression and release of various factors, including P-selectin and CD40 ligand (15).

Conversely, inflammatory stimuli promote clotting through induction of adhesive and procoagulant molecules on endothelial cells and monocytes (16). In most cancer patients, systemic inflammation is reflected by laboratory evidence of an acute-phase reaction, as indicated by elevated levels of fibrinogen and C-reactive protein, and becomes microscopically apparent by enhanced infiltration of the tumour microenvironment by lymphocytes, macrophages, and polymorphonuclear leukocytes (4, 5, 17). While inflammation plays a critical role in molecular carcinogenesis (18, 19), as clinically illustrated, for example, by the high incidence of colorectal cancer in patients suffering from ulcerative colitis, malignant tumours are typically referred to as wounds that never heal due to constant irritation of the surrounding organ tissue.

There is convincing evidence from experimental and (pre)clinical studies that tissue factor (TF), the principal initiator of the coagulation protease cascade, is centrally positioned in the above-mentioned triangular network (Fig. 1). Because this position renders TF highly attractive as a diagnostic tool and/or therapeutic target in clinical haematology and oncology, this review will focus on the role of TF in cancer-associated coagulation activation and tumour progression, particularly emphasizing the mechanisms, by which TF promotes blood clot formation.

**Clots in cancer**

**Clinical burden and key events in metastasis?**

Based on the clinical observations of Armand Trousseau (1865), the occurrence of clinically relevant haemostatic abnormalities in cancer patients is typically referred to as Trousseau’s syndrome (20). Although the term comprises a plethora of heterogeneous clotting disorders (21), the most frequently found vascular complication in patients with malignant diseases is venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) and pulmonary embolism (PE). Characteristically, the pathogenesis of cancer-associated VTE affects all aspects of Virchow’s triad (22), including

- alterations in vessel wall integrity,
- blood flow, and
- haemostatic components.

Symptomatic VTE has a negative impact on the cancer patient’s quality of life and is generally associated with an inferior clinical outcome (23). Interestingly, preliminary evidence suggests that the latter also appears to be true for asymptomatic VTE
microenvironment, including stromal fibroblasts, tissue macrophages, and angiogenic endothelial cells (32). There is experimental evidence that TF induction in cancer cells is a direct consequence of defined genetic events, including activating or inactivating mutations of oncoproteins and tumour suppressor genes, respectively (38). For instance, in a murine model of colorectal cancer, activation of k-ras and inactivation of p53 resulted in enhanced tumour cell TF expression (39). Similarly, oncogenic mutations in the gene for the epidermal growth factor receptor (EGFR) may initiate a cascade of intracellular signaling events that eventually result in up-regulated TF production (40,41). Comparable effects on TF gene induction have been reported for a loss of PTEN, which is relevant to the progression of glioblastoma multiforme (42, 43), and formation of the PML-RARα fusion protein, a key event in the molecular pathogenesis of acute promyelocytic leukemia (44).

In some of these studies it was suggested that increased TF expression was not only an epiphenomenon of the genetic transformation process, but that the presence of TF was also highly relevant to tumour biology. For instance, in the murine colorectal cancer model, TF was required for efficient blood vessel formation in implanted primary tumours (39). In glioblastoma multiforme, TF may initiate vasoocclusion due to intravascular thrombosis, which results in local hypoxia and “pseudopalisading” necrosis, thus promoting rapid tumour angiogenesis and aggressive cancer progression (45). More circumstantial evidence was provided by a recent clinical study showing that in non-small-cell lung cancer (NSCLC) patients, tumour levels of TF mRNA were correlated with the mutation status of p53 and PTEN and a significantly shortened overall survival (46).

Most studies using immunohistochemistry on primary tumour samples suggested that enhanced TF expression was associated with a poor histological differentiation, an increased microvessel density (a surrogate marker for tumour angiogenesis), a high frequency of haematogenous metastasis, and an overall unfavorable patient outcome (33–37). From these studies it may be concluded that TF is generally of critical importance to cancer biology. However, several recent studies have questioned the concept that the mere presence of TF on tumour cells is sufficient to drive cancer progression. For instance, the relative contribution of TF expressed on malignant cells versus TF expressed on cells of the tumour microenvironment appears to be highly cancer type and context dependent (47). Furthermore, cancer cell lines that show strong and homogenous TF expression during maintenance culture may severely alter their TF expression profile following xenotransplantation into SCID mice, with subpopulations of tumour cells showing either very strong or hardly any TF expression (40). Finally, transfection of full-length TF into a human pancreatic cancer cell line with no constitutive TF expression may actually inhibit primary tumour growth after xenotransplantation into athymic mice, while transfection of the same cell line with alternatively spliced TF that has negligible procoagulant activity may efficiently promote tumour progression (48,49).

How TF drives cancer progression

It becomes obvious from these observations that the role of TF in cancer biology is far from being conclusively resolved. Likely explanations for the above-described confusing and seemingly discrepant findings are the various potential pathways, by which TF drives tumour progression, and which may be divided into either coagulation-dependent or -independent mechanisms (Fig. 2).

Coagulation-dependent mechanisms include the downstream generation of thrombin, which cleaves fibrinogen to fibrin and strongly activates platelets, thus
contributing to the formation of an extracellular fibrin matrix rich in platelet-derived angiogenic growth factors. However, subcutaneously implanted Lewis lung carcinoma and B16-BL6 melanoma cells appear to develop normally in fibrinogen-deficient mice, suggesting that, at least under some circumstances, fibrin formation is not an absolute requirement for tumourigenesis (50).

Coagulation-independent mechanisms include direct cell signaling of the TF:VIIa and TF:VIIa:FXa complexes through PARs, resulting in enhanced cell proliferation, invasion, and tumour angiogenesis (51, 52). Furthermore, the TF cytoplasmic domain may be directly involved in the expression of vascular endothelial growth factor (VEGF) in tumour cells (53), and TF has been shown to regulate cell migration via interaction with integrin alpha3beta1 and actin-binding protein 280 (54, 55). In this regard it is noteworthy that alternatively spliced TF is also capable of inducing angiogenesis through ligation of various integrins, conferring additional complexity to the issue (56).

Furthermore, coagulation-dependent and coagulation-independent functions of TF in cancer biology may be directly regulated by the redox status of the membrane proximal allosteric disulfide bond within the TF extracellular domain. According to this compelling hypothesis, surface-located protein disulfide isomerase may switch TF from coagulation to PAR-mediated cell signaling (57), potentially offering the possibility to selectively target cellular functions of TF that are relevant to tumour progression without affecting TF-dependent haemostasis. Indeed, a unique monoclonal antibody that specifically interferes with TF-mediated cell signaling, but that has no effect on its procoagulant activity, is capable of significantly delaying tumour growth in vivo (58).

**TF and cancer-associated VTE**

While, despite the mentioned discrepancies and unresolved issues, there is a large body of evidence to suggest a role for TF in cancer progression, fewer studies have investigated the association of tumour cell TF expression with the occurrence of VTE in patients with malignancies. In a small cohort study of 32 consecutive patients with ovarian carcinomas, immunohistochemical TF staining in primary tumours significantly correlated with both VTE, which was diagnosed in 10 patients (31%), and plasma D-dimer (59).

In a large retrospective cohort of 122 patients with pancreatic carcinomas, the rate of VTE was significantly increased in patients with high (VTE rate, 26.3%) as compared to those with low tumour cell TF expression (4.5%) (60). In this study, TF expression in tumours also correlated with histological markers of angiogenesis (i.e. VEGF expression and microvessel density), suggesting an impact of TF expression on tumour biology. Although patients with low TF-expressing carcinomas had a prolonged median overall survival compared to patients whose tumours showed strong TF expression (17.9 versus 12.6 months), this difference failed to reach statistical significance. In contrast, in a recent prospective study on 39 patients with NSCLC, TF expression in primary tumours was not associated with the development of VTE, which occurred in 13% of patients, but was indicative for an advanced tumour stage and a decreased long-term patient survival (61).

**Circulating TF**

With regard to Virchow’s triad, circulating TF is likely to be more relevant to the pathogenesis of cancer-associated VTE than is TF expressed in primary tumours, because it directly mediates blood hypercoagulability. Consequently, over the last decade, numerous studies have been published reporting on circulating TF levels in patients with various types of malignancy-associated clotting disorders. However, for a critical analysis of these studies, it is of utmost importance to consider when, where, and how TF was measured.

**TF measurement**

**Time point**

Several studies have quantified circulating TF during the acute phase of cancer-associated VTE and compared levels to those of an appropriately matched control population (62–66). Although highly suggestive for a pathophysiological role of circulating TF in Trousseau’s syndrome, these studies, by demonstrating a temporal association, provide only circumstantial evidence for its causative involvement. In a small study on 11 pancreatic carcinoma patients, circulating TF was measured during various time points over the course of chemotherapy (67). In the two patients who eventually experienced VTE, levels of circulating TF dramatically increased during the preceding weeks and months, implying a role for TF as a predictive biomarker and further suggesting its causative involvement in cancer-associated VTE.

Similarly, in a retrospective analysis of cancer patients who initially had no VTE and whose plasma samples were analyzed for TF-positive microparticles (MPs) by impedance-based flow cytometry, the one-year cumulative incidence of VTE was almost 55% in patients with TF-positive MPs as compared to 0% in patients without detectable TF-positive MPs (68). Likewise, in a cohort of five patients with cancer-associated DIC, effective anti-tumour therapy in two patients resulted in both resolution of overt systemic coagulopathy and a significant decline in circulating TF levels, providing an additional causative link between the latter and activation of haemostasis (69).

**Compartment**

In cancer patients, TF may circulate in association with cells and MPs or as a soluble (i.e. alternatively spliced) variant. Induction of cellular TF has been conclusively shown for blood monocytes, whereas TF synthesis by granulocytes, lymphocytes, and platelets is still a matter of debate (70). However, the latter cell types may adsorb MP-associated and/or soluble TF variants and thus contribute to the pathogenesis of cancer-associated clotting disorders. Most recent studies on circulating TF in cancer patients have focused on plasma MPs, which are considered highly relevant for both haemostasis and thrombosis (71). MPs are small membrane vesicles of usually <1 μm in diameter that are shed into the circulation from non-transformed cells upon activation or induction of
apoptosis. In contrast, spontaneous shedding of MPs is a characteristic feature of cancer cells (72).

Besides TF, MPs may carry a variable amount of negatively charged phospholipids (i.e. phosphatidylserine) on their membrane surfaces, making them to key mediators of procoagulant activity in vitro and in vivo. There is a convincing body of independent evidence in the literature to suggest that levels of MP-associated TF are increased in patients with cancer and correlate with both markers of systemic coagulation activation (i.e. plasma D-dimer) and clinically overt clotting disorders such as VTE or decompensated DIC (62–74). However, hardly any data is available on how the magnitude of MP-associated TF compares to the magnitude of TF expressed on circulating monocytes or tumour cells.

Consequently, it is currently unclear, if TF-bearing MPs simply represent a surrogate marker for the cellular pool of circulating TF, which might be pathophysiologically more relevant.

Method

Circulating TF may be detected and quantified on its activity or antigen level (75). Functional approaches include clotting, chromogenic, and thrombin generation assays, whereas enzyme-linked immunosorbent assays (ELISAs) and (impedance-based) flow cytometry are mainly used to study its antigenic expression. In general, assays measuring TF activity are considered more sensitive and specific and, recognizing that TF may reside on cells and MPs in a functionally cryptic state, more (patho)physiologically relevant than antigenic assays. Particularly, depending on the types (monoclonal versus polyclonal) and specificities of antibodies used, commercial ELISAs may capture and detect both MP-specificities of antibodies used, commercial ELISAs may capture and detect both MP-specificities of antibodies used, commercial ELISAs may capture and detect both MP-specificities of antibodies used, commercial ELISAs may capture and detect both MP-specificities of antibodies used, commercial ELISAS may capture and detect both MP-...
able information about the biology of the parental tumour, it is not conclusively established, if MPs are directly involved in tumour progression. MPs may horizontally transfer growth factors, TF, and other signalling molecules as well as nucleic acids between cells of the tumour microenvironment (82), but convincing in-vivo evidence that these properties are relevant to tumour growth and metastasis is still lacking. Nevertheless, TF-positive MPs represent an attractive sub-cellular link between hypercoagulability, inflammation, and disease progression. For instance, in patients with localized prostate cancer, circulating MP-associated TF activity, most likely derived from primary tumour tissues, significantly correlated with both plasma D-dimer and laboratory evidence of an acute-phase reaction (74).

**TF and metastasis**

**Role of tumour cell TF**

Haematogenous metastasis is the result of a tightly regulated cascade involving the invasion of preexisting or angiogenic blood vessels by the tumour, survival of cancer cells within the circulation, and their extravasation at sites of vascular lodgment. Due to the complexity of these events, blood-borne metastasis is considered a highly inefficient process. Particularly, survival of tumour cells within the blood is severely hampered due to effective immune surveillance by cytotoxic T cells.

Almost 20 years ago, first in-vivo evidence was provided that TF promotes experimental lung metastasis through its procoagulant activity (83). Over the following two decades it has become clear that this pro-metastatic function of tumour cell TF is mainly related to downstream thrombin generation, fibrin formation, and platelet activation rather than to upstream PAR-1 or PAR-2 signaling (Fig. 2) (1, 27). According to the current understanding of experimental lung metastasis, initial adherence of intravenously injected cancer cells to the target organ microvasculature is not the limiting step of successful tumour nodulation. In contrast, subsequent clearance of cancer cells lodged in the lung microcirculation profoundly depends on whether the haemostatic system is competent or not. It has been conclusively shown that formation of a fibrin(ogen)-platelet clot around tumour cells facilitates both their spreading on the vascular endothelium and their protection from natural killer (NK) cell-mediated cytotoxicity (84,85). Although circulating tumour cells may directly activate platelets via shear stress-dependent, adhesive mechanisms, platelet stimulation secondary to tumour cell-induced thrombin generation is thought to be predominantly involved in this process. Consequently, pharmacological inhibition and/or genetic disruption of the haemostatic cascade, ranging from TF-initiated coagulation activation to fibrin formation and platelet aggregation, have been shown to effectively suppress experimental lung metastasis in mice (86).

In virtually all of the studies using pharmacological approaches, animals were treated before or immediately after tumour cell injection, suggesting that haemostatic competence within the first few hours is most critical to blood-borne metastasis. Indeed, by using intravital microscopy, Im and co-workers (84) convincingly demonstrated that platelet aggregates surrounding cancer cells lodged in the lung microcirculation were completely resolved within six hours after tumour cell inoculation. It thus appears that the fate of a circulating tumour cell strongly depends on its capac-

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**Fig. 3** Hypothetical contribution of circulating microparticle (MP)-associated tissue factor (TF) to haematogenous metastasis

*a)* After small-vessel injury, extravascular TF initiates coagulation, but becomes rapidly separated from the flowing blood by the growing platelet thrombus. In this phase, recruitment of TF-bearing MPs maintains initiation of the intrinsic coagulation pathway and thus contributes to thrombus propagation.

*b)* Similar events may take place in tumour cell-induced microvascular thrombosis, which is considered highly relevant to haematogenous metastasis.

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ity to initiate microvascular thrombosis, and that both anticoagulants and anti-platelet agents are capable of interfering with this process (86). In contrast, once a tumour cell has escaped immunosurveillance and initiates clonal growth at the site of vascular lodgment, targeting the haemostatic system appears to be far less of an effective anti-metastatic strategy.

Recently, evidence has emerged that non-anticoagulant heparin compounds may also be effective inhibitors of experimental lung metastasis (87). Furthermore, the anti-metastatic potential of fondaparinux, a synthetic pentasaccharide, and various unfractionated and low-molecular-weight heparin preparations appeared to be highly variable despite similar anticoagulant activity (88). These findings are most likely explained by the different potencies of the drugs to liberate TF pathway inhibitor (TFPI) from endothelial cells and/or to interfere with selectin binding to carcinoma mucins or PSGL-1. Consequently, carcinoma mucins, which may either be expressed on circulating tumour cells and MPs or secreted as soluble molecules, have also been implicated as key players in cancer dissemination and the pathophysiology of Trousseau’s syndrome (21).

MP-associated TF in blood-borne metastasis

Despite strong tumour cell TF expression the intrinsic pathway of coagulation still appears to be important for efficient lung metastasis. For instance, in mice with haemophilia A, a single dose of human factor VIII (FVIII) prior to intravenous tumour cell injection significantly increased the metastatic potential of B16F10 melanoma cells (89). Based on these observations it may be speculated that tumour cell-induced microvascular thrombosis has pathophysiological features that are similar to those of microvascular thrombosis following a circumscribed injury to the vessel wall (90):

In this phase, intravascular TF associated with cellular MPs may be recruited to the growing thrombus via interactions of PSGL-1 with P-selectin, thus further propagating microvascular thrombosis. It is tempting to hypothesize that this model represents a first mechanistic link between circulating TF-bearing MPs and haematogenous metastasis as well as a general explanation for how hypercoagulability promotes cancer dissemination. In fact, pretreatment of wild-type mice with human FVIII, which was likely to increase their plasma thrombin-generating capacity, appeared to render study animals more susceptible to lung metastasis (89). Compared to anticoagulant or anti-platelet strategies, however, far fewer studies have systematically investigated the effects of inherited or acquired hypercoagulability on tumour dissemination (91).

Despite the seemingly convincing role of blood coagulation and platelets in experimental lung metastasis, there is still insufficient evidence to suggest that the same mechanisms take place in patients with cancer. However, pulmonary hypertension caused by a thrombotic microangiopathy caused by embolized tumour cells, as has been described in patients with gastric and ovarian carcinomas, is histopathologically strikingly similar to the microvascular thromboses seen in mice intravenously injected with TF-bearing tumour cells (28–31, 84, 86).

Strategies to target the TF pathway in cancer therapy

Considering the described plethora of (potential) TF functions in tumour biology and cancer-associated VTE, TF may represent a highly attractive therapeutic target in clinical haematology and oncology. So far, the following approaches have been used in experimental and (pre)clinical studies:

- Inhibition of TF procoagulant activity using
  - TFPI (92),
  - monoclonal TF antibodies (83),
  - recombinant nematode anticoagulant protein c2 (rNAPc2) (93), or
  - the tick anticoagulant Ixolaris (94).

- Selective inhibition of TF-initiated, PAR-mediated cell signaling using a monoclonal antibody with no anticoagulant activity (58).

- Down-regulation of TF expression by the delivery of short interfering RNA to tumour cells (95).

- Targeted delivery of cytotoxic drugs or photodynamic therapy to TF-expressing tumour and angiogenic vascular endothelial cells using FVII/FVIIa as a carrier protein (96, 97).

- Induction of cell-mediated cytotoxicity against TF-expressing tumour cells using a human FVII-IgG Fc fusion protein (98).

- Induction of tumour vascular infarction using truncated TF fused to peptide ligands specifically targeting the angiogenic tumour endothelium (99).

Despite promising preliminary results, none of the mentioned treatment modalities is currently applied in routine clinical practice. This may be partially explained by the concern of uncontrolled bleeding in patients receiving anti-TF therapy. However, inhibition of TF in patients with stable coronary artery disease using a potent monoclonal antibody was not associated with major haemorrhagic complications (i.e. a decline in haemoglobin of ≥2 g/dl), albeit spontaneous minor bleeding was observed in a dose-dependent fashion (100). Over the last few years, the enthusiasm about low-molecular-weight heparin (LMWH) as an adjunct to anti-cancer therapy has been slightly dampened by negative preliminary findings and low enrollment rates of recently completed and currently ongoing clinical studies, respectively. Among other reasons, the latter could be due to the fact that there is still no conclusive mechanism on how LMWH exerts its antineoplastic effects, which are likely due to a complex modification of the tumour microenvironment.

From an oncologist’s standpoint, anti-TF treatment of selective tumour types and patient subgroups may be more in line with the modern concept of individualized, targeted anti-cancer therapy.
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