Platelets in cancer and thrombosis

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Summary
Platelets are the smallest circulating blood cells and their major function is the maintenance of haemostasis. They do not have a nucleus, but instead a multitude of granules that contain molecules important for several physiological processes. These granules can be released after platelet activation and thereby platelets take part in haemostasis, wound repair or immunological processes. Furthermore, platelets are also involved in the pathophysiology of several diseases, including cancer. Platelets can support various steps of cancer development and progression by promoting tumour growth, angiogenesis and metastasis. Moreover, platelets contribute to the hypercoagulable state frequently observed in cancer patients, leading to an increased risk of venous thromboembolism (VTE). In previous studies a high platelet count was repeatedly found to be associated with an elevated risk of VTE and a worse prognosis in patients with cancer. The aim of this review is to give an overview of the most important alterations of platelet physiology in cancer patients and how these alterations may influence cancer disease and contribute to cancer-associated VTE.

Platelets are the smallest circulating haematopoietic cells. They derive from fragmentation of the plasma membrane of megakaryocytes in the bone marrow. Platelets possess no nucleus and therefore their capacity of protein synthesis is limited. However, they are packed with numerous organelles that contain molecules important for various physiological processes including haemostasis, wound repair or immunity. Their small size is compensated by their large number: With a reference range of 150 000–350 000/µl they are the second most frequent blood cells after red blood cells.

Platelets are best known for their role in haemostasis, as their major function is the formation of blood clots in case of a vessel wall injury. However, besides this vitally important physiological function, they are also involved in the pathology of a number of diseases, such as vascular thrombotic disorders, inflammatory diseases and also cancer (1). The role of platelets in cancer and also in venous thromboembolism (VTE), which is a frequent complication in patients with cancer, is multifaceted and has already been intensely investigated. The key facts about the association between cancer and platelets are:

- Elevation of platelet counts, i.e. thrombocytosis, is frequently found in patients with cancer (2).
- Patients with cancer have an increased risk of VTE – especially cancer patients with thrombocytosis (3).
- Thrombocytosis is associated with poor prognosis in many types of cancer (4).
- Experimental reduction in platelet numbers or inhibition of platelet function have shown anti-metastatic effects in animal models (5).
- Anti-platelet drugs such as aspirin have been shown to have anti-cancer effects (6).
This review focuses on the bidirectional influences of cancer on platelet physiology and, vice versa, on influences of platelet behaviour on cancer, principally with respect to solid tumours.

The influence of cancer on platelet behaviour

Thrombocytosis in cancer

The most obvious and longest known alteration of platelet physiology that occurs in patients with cancer is the frequently observed increase in platelet numbers in these patients. Already in 1872 this phenomenon was noted by Leopold Riess (7). In a more recent study of 3003 patients with different types of cancer, thrombocytosis – defined by a platelet count of more than 350000/µl – was found in 22% of patients (2).

Thrombocytosis is a well described factor of poor prognosis in the majority of solid tumours; reviewed in (4).

Since reactive thrombocytosis is commonly found in inflammation and infection and since cancer also constitutes a pro-inflammatory condition, thrombocytosis could be regarded as an epiphenomenon of inflammation in cancer. However, several authors consider thrombocytosis as an independent paraneoplastic syndrome (8–10):

Underlying mechanisms of this phenomenon are considered to be based on increased cytokine levels; interleukin (IL)-1, IL-6 or granulocyte-colony-stimulating factor were proposed to play an important role (9). In a recent study that investigated thrombocytosis in ovarian cancer, tumour cells were found to produce IL-6, which induces the production of thrombopoietin (TPO) in the liver. TPO then leads to increased platelet production in the bone marrow, resulting in elevation of platelet counts. These elevated platelet counts where shown to further fuel tumour growth, which again stimulates thrombopoiesis – a paracrine circuit was proposed (10). However, in contrast to this findings, Simanek et al. found no correlation of platelet counts with TPO levels in a cohort of 665 patients with different types of solid tumours (3).
Therefore, the role of these markers in cancer progression does not seem to be entirely clear and their clinical significance for the prognosis of disease remains largely unknown.

The most extensively studied marker of platelet activation is soluble P-selectin (sP-selectin). After expression of P-selectin on the platelet surface upon activation, it becomes proteolytically cleaved and a soluble part is released into the circulation: sP-selectin. Although P-selectin is also expressed by other cells, sP-selectin was proposed to be a reliable marker of in vivo activation of platelets (24). Several studies found that higher

<table>
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<tr>
<th>marker</th>
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<tr>
<td>soluble P-selectin</td>
<td>60/60 breast, prostate higher in cancer patients</td>
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<td>41/41 breast</td>
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<td>116/59 lung</td>
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<td>higher levels associated with late stage squamous cell carcinoma (not adenocarcinomas)</td>
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<td>181/181 colorectal</td>
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<td>• higher in patients with metastatic disease</td>
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<td>no correlation with lymph node metastasis</td>
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<td>no correlation with tumour stage, no normalization 3 months after nephrectomy</td>
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<td>CD40 ligand</td>
<td>120/60 lung</td>
<td>higher in cancer patients</td>
<td>• higher in squamous cell carcinoma than in adenocarcinoma</td>
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<td>• higher levels in metastatic disease of squamous cell carcinoma (not adenocarcinomas)</td>
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<td>10/12 pancreas, colorectal no difference</td>
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<td>62/62 pancreas</td>
<td>high levels associated with poor prognosis and risk of VTE</td>
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<td>35/84 colon</td>
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<td>37/30 lung</td>
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<td>β-thromboglobulin (β-TG)</td>
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<td>52/24 kidney</td>
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<td>aggregometry</td>
<td>47/55 breast</td>
<td>platelet aggregation in response to thrombin higher in cancer patients</td>
<td>Platelet aggregation in response to thrombin increases during chemotherapy</td>
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<td>9 patients (4 with metastasis)</td>
<td>platelet aggregation in response to collagen significantly higher in metastatic cancer patients compared to non-metastatic disease</td>
<td>No significant difference in platelet aggregation in response to thrombin, but maximal aggregation response to thrombin was significantly higher in metastatic patients</td>
<td>97</td>
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Tab. 1 Platelet activation in patients with cancer: relevant studies
levels of sP-selectin can be found in the circulation of patients with cancer in comparison to healthy individuals (▶Tab. 1).

Platelet size, measured by the mean platelet volume (MPV), has also been proposed to be a marker of platelet activity, as it was found to correlate with in vitro platelet activation; and a high MPV was reported to be associated with cardiovascular diseases in non-cancer patients (25). However, in patients with cancer we found mean MPV levels to be slightly lower in a cohort of 1544 patients with different types of cancer in comparison to 65 age- and sex-matched healthy controls (26). In contrast to studies of patients with cardiovascular disease, in patients with cancer a high MPV was associated with decreased VTE risk and improved survival (26). Hence, the role of MPV in cancer remains to be further elucidated.

Platelet microparticles

During the process of activation, platelets not only release various single molecules into the circulation, but also shed vesicles with membrane receptors and cytoplasmic proteins, so-called microparticles (MPs), from their plasma membrane. MPs are defined as small membrane vesicles with a diameter between 0.1–1.0 mm that have a negatively charged phosphatidylserine (PS)-rich surface. They can be shed from various cells upon cell activation or apoptosis, including platelets, erythrocytes, endothelial cells, leukocytes, monocytes, smooth muscle cells and also cancer cells (27). However, the majority of circulating MPs (approximately 80%) is suggested to derive from platelets (28). Growing evidence indicates that MPs are involved in tumour growth, as they can support angiogenesis, cancer cell invasion and suppress the host immune response against the tumour. Moreover, their negatively charged and extremely procoagulant surface may also promote the hypercoagulable state observed in cancer patients (27). Increased levels of MPs were found in patients with cancer compared to healthy controls in a study conducted by our group. However, levels of circulating MPs measured at study inclusion were not found to be significantly different in cancer patients who developed VTE compared to those who did not develop VTE during the course of their disease (29).

Studies that particularly investigated platelet-derived MPs (PMPs) found that PMPs carry cellular growth factors, promote cell proliferation and survival and enhance lung metastasis formation in mice. In in vitro studies PMPs were found to increase the adhesive properties of cancer cells to endothelial cells. Further, PMPs were found to carry a number of growth factors and factors promoting angiogenesis (30).

- In clinical studies, PMPs were found to be higher in cancer patients than in healthy controls, and particularly high in cancer patients who had developed VTE (31).
- In breast cancer PMPs were found to be higher in patients with large local tumours or metastatic disease than in women with small or benign breast tumours (28).

These findings suggest that PMPs may play an important role in cancer and induce a procoagulant state. However, at the current state the role of PMPs as diagnostic or prognostic markers in patients with cancer is not exactly elucidated.

The impact of platelets on cancer

Platelets in tumour development and growth

Aspirin as a cancer-preventive agent

Aspirin is for sure the most prominent and most widely used anti-platelet drug. The drug acts as an inhibitor of platelets’ thromboxane synthesis, which is an important molecule for platelet activation. Aspirin is widely used for the prevention of atherothrombotic diseases such as coronary artery disease or stroke and for these indications it has been extensively studied in large clinical trials.

Interestingly, recent analysis of data from these trials revealed that people who regularly took aspirin had an approximately 25% lower short-term risk for several types of cancer (6) as well as a reduced risk of colorectal cancer after 20 years follow-up compared to control groups (32).

A cancer-preventive effect of aspirin was also previously described (33). However, the more recent studies have shown that this effect is already present at low-doses of aspirin, starting from 75 mg daily.

Since the mode of action of low-dose aspirin is thought to be based on its anti-platelet effects, these data suggest that platelets may play a role in the development of cancer (34, 35). Similar observations were also found in an animal model investigating the development of hepatocellular carcinoma (HCC) in mice with chronic hepatitis B. In this model, anti-platelet therapy with low-dose aspirin was shown to prevent the development of HCC (36). Interestingly, this effect was only present in immune-mediated HCC associated with chronic hepatitis B, whereas anti-platelet therapy did not prevent the induction of non-immunologically induced HCC by exposure to hepatotoxic chemicals. The role of platelets in tumour initiation could therefore be related to immunological processes.

Clopidogrel, an anti-platelet drug, which is also extensively used for cardiovascular diseases, lowers platelet function via inhibition of the platelet ADP receptor and was, in contrast to aspirin, found to have no effect on cancer mortality (37).

Platelets and growth of the primary tumour – cancer cell proliferation

Literature about the direct influence of platelets on cancer cell proliferation is conflicting. While some in vitro studies found that platelets reduce cancer cell proliferation, either by cytotoxic effects (38, 39), induction of apoptosis (40) or cell-cycle arrest to G0/G1 phase (41), other studies found a rather stimulatory effect of platelets on cancer cell proliferation (42).

In one study, platelets were found to enhance ovarian cancer cell growth via a transforming growth factor (TGF)-β dependent mechanism (42). Platelets are the major source for TGF-β in the circulation. Furthermore, one in vitro study investigated whether platelets could influence the efficacy of chemotherapeutic substances on cancer cells. It was found that co-incubation of cancer cell lines with platelets increased survival of human adenocarcino-
ma cells that were challenged with the widely used chemotherapeutic agents 5-fluorouracil and paclitaxel. In this study, platelets were found to inhibit apoptosis, reverse the cell cycle arrest induced by anticancer-drugs and enhance DNA repair of cancer cells. The authors conclude that platelet-cancer cell interactions provide a potential target to reduce chemoresistance of cancer cells (43).

Platelets and tumour angiogenesis

It was first postulated in 1971 that tumour growth is dependent on the formation of new blood vessels (44). Platelets are carriers of a variety of factors that are involved in the regulation of angiogenesis, both pro- and anti-angiogenic factors. These factors are stored in the so-called a granules of platelets, where also coagulation factors or adhesion proteins are contained, and are released after platelet activation.

- Amongst the proangiogenic factors is the most prominent and also most important factor for angiogenesis, vascular endothelial growth factor (VEGF), but there are also other molecules such as basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF-1), platelet-derived growth factor (PDGF).
- Anti-angiogenic factors stored in platelets include, for example, thrombospondin 1 (TSP-1), platelet factor 4 (PF-4), endostatin or angiostatin (9).

Although these pro- and anti-angiogenic factors are both contained inside platelets, the net effect of platelets on angiogenesis was found to be a supportive one, i.e. platelets were found to enhance angiogenesis (45). In addition to the release of angiogenic factors from their granules, platelets were demonstrated to have a supportive effect on angiogenesis by preventing excessive haemorrhage from newly formed vessels through their adhesive properties (45).

An intriguing question was how platelets could regulate angiogenesis, since they contain both pro- and anti-angiogenic proteins. A close look on platelets a granules in a study published by Italiano et al. revealed that pro- and anti-angiogenic factors are stored in separate and distinct a granules of platelets (46). This study also showed that these differentially packed granules could be separately released. Activation of platelets via the

- thrombin receptor protease-activated receptor (PAR)-4 resulted in a release of granules packed with anti-angiogenic proteins,
- thrombin receptor PAR-1 liberated VEGF-containing, pro-angiogenic, granules.

In subsequent studies conducted by the same group also cancer cells were found to induce differential release of angiogenic factors from platelets (47).

Cancer cells specifically induced the release of VEGF from a granules, which promoted angiogenesis.

Interestingly, aspirin suppressed the release of VEGF from platelets stimulated by cancer cells, providing one possible explanation of how aspirin exhibits anti-cancer effects (47).

On the other hand, platelets also contain anti-angiogenic factors and studies have reported that these are important in suppressing tumour angiogenesis. This observation is supported by studies of mice lacking the angiogenesis inhibitor TSP-1 – these mice were found to have increased tumour angiogenesis and growth (48).

In conclusion, a specific modulation of platelet function and granule release could be a promising therapeutic option in terms of anti-angiogenic therapy with eventually more success than a general, unspecific inhibition of platelet function, which might increase the risk of bleeding.

Another interesting finding from studies investigating angiogenic factors in platelets in malignancy is that platelets were found to have the ability to actively sequester these factors (49). Analysis of platelet protein contents revealed that tumour-bearing mice have altered levels of the angiogenesis regulators PP-4 and TSP-1 in their platelets in comparison to control mice. Interestingly, these alterations are already present at very early stages of tumour development, when cancers are only microscopically detectable, which could render the platelet protein contents to be potential biomarkers of early tumour growth (48, 50).

Platelets and tumour spread

In contrast to the not completely understood influence of platelets on the growth of the primary tumour, evidence supporting a promotional effect of platelets on metastasis formation is compelling; reviewed in (5, 51). Already in 1968 Gasic et al. observed that a reduction in platelet counts in mice led to a distinct reduction in lung metastasis formation (52). These results could be reproduced by other studies. Camerer et al. showed that genetically modified mice, which have virtually no circulating platelets, are remarkably protected against haemogenous metastasis. Moreover, mice that lack the thrombin receptor PAR-4 and consequently cannot be activated by thrombin, showed reduced metastasis formation (53). In further studies using different knock-out mouse models other platelet molecules, such as the surface glycoproteins GPIba (54) or GPIV (55), were found to be involved in metastasis formation.

Very interestingly, Zhang et al. developed a novel anti-platelet antibody that preferentially binds to activated platelets and induces fragmentation of these cells (56). During platelet activation the fibrinogen receptor GPIIb/IIIa undergoes a conformational change and this antibody specifically targets the activated form of GPIIb/IIIa, which results in lysis of activated platelets. Mice treated with this antibody were protected against lung metastasis formation while haemostatic functions were not affected. Although these characteristics seem promising, the therapeutic application could be challenging, since the antibody is effective only a few hours before and after the administration of tumour cells into the circulation of the mice, i.e. at the very beginning of metastasis formation (57).

Several studies could provide insights into underlying molecular mechanisms about how platelets promote metastasis. First, platelets were found to shield circulating tumour cells against the immune system, whereby they attenuate the function of natural killer cells (58). In recent
studies it could be shown that platelets also play an important role in extravasation of circulating tumour cells and formation of new metastatic foci. ATP (adenosinetriphosphate), which is stored in platelets' dense granules and released after platelet activation, was found to open the endothelial barrier and to consequently enable tumour cells to extravasate (59). For extravasation, the tumour cells need to invade the tissue to enable metastasis. Also in this process platelets were suggested to be involved, as they were shown to be able to induce epithelial-to-mesenchymal transition (EMT), a process in which tumour cells with an epithelial phenotype acquire properties of mesenchymal cells. This process is important in tumour cell invasion and the formation of new metastatic foci. Platelets may directly, via cell-cell-contact, and indirectly, via the release of TGF-β, induce EMT (60).

Further evidence for the role of platelets in cancer metastasis again comes from follow-up analyses of randomized clinical trials that originally investigated the effect of aspirin vs. placebo in cardiovascular diseases. Analysis of data from patients included in these studies showed that those patients who regularly took aspirin and who developed cancer had a significantly lower risk of distant metastasis compared to the control group. The risk of metastasis at the time of initial cancer diagnosis as well as the risk of developing metastasis during the course of the cancer disease were reduced in the aspirin group. The authors suggest that aspirin might have not only a preventive effect on metastasis formation prior to the diagnosis of cancer but also a therapeutic, anti-metastatic effect in patients already diagnosed with cancer (61). However, randomized, controlled trials that investigated the therapeutic effects of anti-platelet drugs in the treatment of cancer are so far scarce and came to inconclusive results.

Aspirin and also mepipadomole (a dipryridamole derivate, which decreases platelet aggregation) improved survival of cancer patients in some studies, whereas in other clinical studies no effect of anti-platelet agents on the survival of patients with cancer was found; reviewed in (62).

Further well-designed studies are warranted to clarify the inconsistency with regard to the effect of specific platelet inhibition on the prognosis of patients with cancer.

**Platelets and the development of cancer-associated VTE**

Cancer is known to be associated with a hypercoagulable state. The most apparent sign of an increased activation of the coagulation system is the observation that patients with cancer have an increased risk of VTE. The actual risk for patients with cancer to develop VTE varies between 0.5 and 20% per year, depending on the type of cancer and several tumour-, therapy- and patient-related factors (63). Tumour entities associated with a high risk of VTE are gastric, pancreatic, kidney or lung cancer, as well as glioblastoma, lymphoma or myeloma. Therapy- and patient-related factors associated with a higher risk of VTE include, for example,

- surgical procedures,
- chemotherapy,
- immobilisation,
- high body weight and
- co-morbidities.

Several laboratory parameters were found to predict the risk of VTE in cancer patients. Besides low haemoglobin levels or high leucocyte counts, interestingly, also a high platelet count is one of these parameters (64, 65). Moreover, high levels of the platelet activation marker sP-selectin were found to be associated with an increased risk of VTE in patients with cancer (66).

Based on these findings it can be suggested that platelets are substantially involved in the development of cancer-associated VTE.

In general, the role of platelets in the development of thrombosis in the venous system was long thought to be of minor importance. In early investigations venous thrombi were described to be platelet-free, in contrast to the platelet-rich arterial thrombi (67). While the pathophysiology of arterial thrombosis is largely mediated through platelets and their attachment to injured vessel walls in a high shear stress system, thrombosis in the venous system is proposed to occur over intact endothelium through multifactorial processes including alterations of blood flow, coagulation factors and the vessel wall (68). However, platelet aggregation has long been known to be involved in the development of venous thrombosis and platelets are actually found also in venous thrombi (69).

Several mechanisms of platelet involvement in venous thrombosis have been proposed. Importantly, activated platelets expose negatively charged phospholipids and thereby exhibit a procoagulant surface. Through this procoagulant surface platelets can induce the generation of thrombin, which is a key enzyme of the coagulation system that leads to the formation of fibrin and clots (70). Furthermore, it could be shown that platelets and the interaction between platelet GPIba and von Willebrand factor are necessary for experimental induction of thrombosis in the inferior vena cava of mice (71). Clinical studies demonstrated that soluble P-selectin is elevated in patients with acute VTE and that higher sP-selectin is a risk factor for VTE, proposing sP-selectin as a possible biomarker for the diagnosis of VTE and suggesting that platelet activation may be involved in the development of VTE (72).

Interestingly, in clinical trials anti-platelet therapy with aspirin has been reported to be effective also in the prevention of VTE after total hip arthroplasty and secondary prophylaxis of unprovoked VTE (73–75). While platelet inhibitory agents might be considered in the prevention of VTE, there is no obvious indication for platelet inhibition in the treatment of VTE.

In the cancer setting, aspirin is used for primary prophylaxis of VTE in patients with multiple myeloma who are treated with thalidomide or lenalidomide in combination with chemotherapy and/or dexamethason.

As these patients have a high risk of VTE, primary thromboprophylaxis is recommended – for this purpose aspirin turned out to be as effective as low-molecular weight heparin (LMWH) in a randomized
controlled trial (76). Apart from this specific indication, anti-platelet therapy is not used in the prevention of cancer-associated VTE.

However, platelet parameters are included in risk prediction models of VTE in cancer patients. For instance, a high platelet count is one of three laboratory parameters that are incorporated together with clinical parameters in the so-called Khorana-score, a risk prediction model for VTE in cancer patients (65). This score has been confirmed and could be refined with respect to a more accurate risk stratification of VTE by adding two further laboratory parameters: D-dimer and sP-selectin, a platelet biomarker (64). Whether other platelet biomarkers may also help to predict the risk of VTE in patients with cancer remains to be investigated. So far, one clinical study found that high serum levels of PF-4 are associated with an elevated risk of VTE in patients with pancreatic cancer (77).

**Conclusions**

Platelets play a considerable role in cancer, as they influence the progression of cancer and are associated with the development of cancer-associated VTE ( ► Fig. 1). Cancer leads to changes in platelet behaviour, resulting in an elevation of platelet counts and in the activation of platelets. Furthermore, an elevated platelet count is a negative prognostic factor in most types of cancer and experimental reduction in (activated) platelets in mouse models has been found to protect against metastasis formation. These findings have several important clinical implications.

- Alterations of platelet parameters in cancer patients could represent potentially useful biomarkers for early cancer diagnosis, prognosis of disease and for the risk of VTE. This hypothesis is supported by data from experimental studies that found platelet protein contents to be altered in tumour-bearing animals already at very early stages of tumour growth (50). Furthermore, an elevated platelet count has been included in a risk scoring model for predicting VTE in cancer patients. This risk score has been recommended to be considered by clinicians for risk stratification for VTE in cancer patients in the latest guidelines of the American Society of Oncology (78). Other platelet biomarkers such as sP-selectin (66) have also been found to be predictive of VTE in cancer patients and could possibly add to an improved risk stratification.
- The finding that platelets interact with cancer cells and promote cancer progression obviously offers a potential option for therapeutic interventions. Data from large clinical trials suggest that the anti-platelet drug aspirin reduces the incidence and mortality of several types of cancer, as well as the risk of metastasis formation (6, 61). Preclinical and clinical studies have reported that anti-platelets drugs could improve cancer outcomes. Whether aspirin or other anti-platelet drugs might be used for therapy or even for primary prevention of cancer requires further investigations.
- Platelet involvement in cancer-associated VTE also provides potential drug targets for antithrombotic therapy.

The main challenge in the development of therapies interfering with platelet-cancer-cell interactions will be to find drugs that inhibit the roles of platelets in cancer promotion and development of VTE without suppressing their important physiological functions needed for the arrest of bleeding.

**Personal view and perspectives**

Considering this relatively huge body of evidence, platelets are important contributors to the pathophysiology of cancer and thrombosis. The question will be how to use this information and translate it to clinical applications.

Platelet alterations offer chances for identification of platelet-specific biomarkers for cancer diagnosis, prognosis and development of VTE. The potential use of such markers for clinical routine is currently limited due to a variety of factors. First of all, analytical methods are not standardized and currently also not available for clinical routine (e.g. for measurement of sP-selectin). Another big issue in measuring markers of platelet activity is the risk of ex vivo platelet activation due to blood sampling. Furthermore, at the current state it is not clear, which markers can be used since studies came to conflicting results, also concerning different types of cancer. To our opinion, the currently best-established platelet biomarker is sP-selectin, for which a multitude of clinical studies exist and which was shown to be associated with risk of VTE in cancer patients.

Furthermore, platelets offer potential drug targets for anti-cancer and anti-
thrombotic therapy. Data from animal models are convincing, however, clinical studies came to conflicting and not entirely promising results. More detailed characterisation of the interaction between platelets and cancer could help in the identification of optimized targets. Moreover, it seems to be very likely that the role of platelets in tumour development differs in different types and stages of cancer. Platelets may enhance metastasis formation – however, it is unclear at what time during the disease and how this connection can be interrupted in the clinic. Further research is needed to better understand the platelet behaviour in patients with cancer in order to eventually use anti-platelet therapy in the future as a double-hit strategy to prevent thrombotic events and improve survival in patients with cancer.

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Conflict of interest

The authors declare that they have no conflict of interest.

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