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REVIEW

Platelet–cancer interactions: mechanisms and pharmacology of tumour cell-induced platelet aggregation

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During haematogenous metastasis, cancer cells migrate to the vasculature and interact with platelets resulting in tumour cell-induced platelet aggregation (TCIPA). We review:

1 The biological and clinical significance of TCIPA;

2 Molecular mechanisms involved in platelet aggregation by cancer cells;

3 Strategies for pharmacological regulation of these interactions.

We conclude that pharmacological regulation of platelet–cancer cell interactions may reduce the impact of TCIPA on cancer biology.
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Keywords: Platelet aggregation; cancer; tumour; metastasis

Abbreviations: ADP, adenosine diphosphate; BM-567, {*N*-terbutyl-*N*′-[2-4′-methylphenylamino)-5-nitro-benzenosulphony]-urea}; GP, glycoprotein; 12-HETE, 12-hydroxyeicosatetraenoic acid; MMP, matrix metalloproteinase; NO, nitric oxide; OKY-046, (E)-3-[*p*-(1H-imidazolomethyl)-phenyl]-2-propenoic acid; PAR, proteinase-activated receptor; PSGL, P-selectin glycoprotein ligand; SQ-29,548, [1S-1α,2α(Z),3α,4α]]-7-[3-[[2-[(phenylamino)carbonyl]hydrazine]methyl]-7-oxabicyclo[2.2.1]hept-2-yl-5-heptenoic acid; TCIPA, tumour cell-induced platelet aggregation; TIMP-4, tissue inhibitor of metalloproteinase-4; TXA_2, thromboxane A_2; XV454, 3-[4[(aminomethyl)phenyl]-4,5-dihydro-5-isox-azolyl]acetyl]amino]-*N*-[(3-methylphenyl)sulphonyl]-L-alanine

Introduction

Circulating platelets are best known for their contribution to vascular haemostasis, thrombosis, atherosclerosis and inflammation (Ginsberg *et al*., 1988; Bazzoni *et al*., 1991; Celi *et al*., 1997; Radomski & Radomski, 2000; Schwarz *et al*., 2001; Alonso & Radomski, 2003). However, the interactions between platelets and cancer cells are less appreciated. This is somewhat surprising considering that blood vessels are major anatomical pathways for cancer cell dissemination. Within the vasculature circulating cancer cells interact with endothelial cells, leukocytes and platelets.

The association between abnormalities of haemostasis and cancer clinically known as recurrent migratory thrombophlebitis was first reported by Professor Armand Trousseau, as early as in 1865 (Trousseau, 1865). Trousseau described 182 cases of primary thrombophlebitis occurring in occult malignancies. In this group of patients, he emphasized the association of malignancies with pathological findings such as the formation of venous and arterial platelet-rich microthrombi in the vasculature. Since the original Trousseau paper numerous clinical and pathological observations confirmed the increased risk of thrombosis in patients with cancer and highlighted the involvement of activated coagulation and fibrinolytic systems in the genesis of cancer (Zacharski *et al*., 1986; 1992; Loreto *et al*., 2000; Levine & Lee, 2001; Rickles & Falanga, 2001; Rickles *et al*., 2001; 2003; Zacharski, 2002; Caine *et al*., 2003; Kakkar, 2003a, b; Lee & Levine, 2003; Lee *et al*., 2003a; White, 2003).

This activation can be initiated by a large number of factors such as direct generation of thrombin by cancer cell procoagulants; thrombin generation by cancer cell-stimulated host cells, damage to normal tissue from tumour masses, infection, tissue necrosis, introduction of mucin into the circulation, surgical trauma, chemotherapy toxicity and effects of venous access devices (Zacharski *et al*., 1992; Rickles *et al*., 2001; Zacharski, 2002). The procoagulants including tissue factor (TF), fibrinogen, activated factors VII, X and XII and thrombin can also affect cancer growth (Zacharski *et al*., 1992; Rickles *et al*., 2001; Zacharski, 2002). Moreover, anticoagulant treatment with heparin has been shown to reduce the risk of venous thromboembolism (Lee *et al*., 2003b).

Interestingly, cancer cells can express on their surface all the factors involved in regulation of fibrin. This expression affects not only the coagulation–fibrinolysis balance, but also plays a role in tumour invasion, proliferation, and metastasis (Kwaan & Keer, 1990; Rickles & Falanga, 2001). In addition to the activation of coagulation and fibrinolysis, the cellular mechanisms involving endothelial cells, monocytes/macrophages and platelets play a vital role in cancer-induced abnormalities of haemostasis. Indeed, blood platelet numbers (platelet count) have been reported to have predictive value in various cancers. High platelet count is associated with poor survival in a large

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variety of cancers including malignant mesothelioma, gynaecological malignancies, lung, renal, gastric, colorectal and breast cancers (Spigel & Mooney, 1977; Nakano *et al*., 1986; Olesen & Thorshauge, 1988; Costantini *et al*., 1990; Hernandez *et al*., 1992; Lopes *et al*., 1994; Zeimet *et al*., 1994; Pedersen & Milman, 1996; 1998; Menczer *et al*., 1998; Hefler *et al*., 2000; Kerpsack & Finan, 2000; Ikeda *et al*., 2002; O'Keefe *et al*., 2002; Taucher *et al*., 2003; Bozkurt *et al*., 2004). The scope of this mini review is limited to the interactions between platelets and cancer cells deriving from solid, but not blood-borne, tumours. These interactions are often called tumour cell-induced platelet aggregation (TCIPA).

Overview of platelet reactions

Platelets are small (approximately 2 μm in size) anucleate blood elements formed from megakaryocytes. Nonactivated (resting) platelets are discoid in shape and contain numerous granules in the cytoplasm (White, 1988). The granules contain agents whose release and function are crucial to platelet reactions. Rheological studies have shown that pulsatile blood flow and shear stress are the major determinants of platelet behaviour *in vivo* (Turitto & Hall, 1998). Shear stress forces platelets to remain close to the endothelium. The biological signal for initiation of platelet haemostasis is delivered by the exposure of adhesive components of the subendothelium that are normally concealed from the blood by the endothelium. Platelets interact with adhesive proteins through adhesion receptors. *In vivo*, under conditions of shear stress, binding of von Willebrand factor to its receptors such as glycoprotein (GP) Ib-IX-V anchors platelets to the subendothelium (Ginsberg *et al*., 1988; 1993). Following an initial contact phase, platelets change shape and spread on the subendothelium. The biological role of aggregation is to reinforce the platelet adhesion monolayer with a structure based on web-like interactions between the adjacent platelets. The aggregate, thus formed, is firm enough to withstand disintegrating stimuli brought about by blood flow and shear forces. The formation of an aggregate requires dramatic rearrangements of platelet structure and cytoskeleton and may be brought about by soluble activator agonists including thrombin, adrenaline, serotonin and ADP. These factors trigger off a biochemical cascade of events that is mediated *via* the release of major mediators from platelets including thromboxane A_2 (TXA_2) (Needleman *et al*., 1976), ADP (Born, 1966) and matrix metalloproteinase-2 (MMP-2) (Sawicki *et al*., 1997). The cascade ultimately leads to the activation of the platelet integrin receptor, GPIIb/IIIa ($\alpha_{IIb}\beta_3$), and this allows binding of fibrinogen to the receptors of adjacent platelets. The binding of fibrinogen results in further reinforcement of the existing platelet plug (Radomski & Moncada, 1993).

In addition to GPIb-IX-V and GPIIb/IIIa, activated platelets express on their surface P-selectin that mediates platelet–leukocyte interactions. P-selectin, a protein of the α granule membrane of resting platelets, is rapidly translocated to the surface during platelet activation (Larsen *et al*., 1989). P-selectin mediates the initial platelet–leukocyte tethering and triggers leukocyte activation *via* interacting with specific carbohydrate ligands on leukocyte P-selectin glycoprotein ligand-1 (PSGL-1) (Moore, 1998).

Tumour cell-induced platelet aggregation

Cancer cells have been shown to aggregate platelets and this ability correlates with the metastatic potential of cancer cells (Gasic *et al*., 1968; 1976; 1978; Karpatkin *et al*., 1981; Pearlstein *et al*., 1981; Gasic, 1984; Radomski *et al*., 1991). The ability of malignant tumour cells to aggregate platelets, that is, tumour cell-induced platelet aggregation (TCIPA) confers a number of advantages to the survival of the tumour cell in the vasculature and in its successful metastasis. When covered with a coat of platelets, a tumour cell acquires the ability to evade the body's immune system. Indeed, it has been shown that platelets protect tumours from TNF-α-mediated cytotoxicity (Philippe *et al*., 1993; Shau *et al*. 1993). In addition, platelets may shield cancerous cells from high shear forces seen in flowing blood that could potentially damage the tumour cell. Another survival advantage for the tumour cell is the tendency for the large tumour–platelet aggregate to embolize the microvasculature at a new extravasation site (Malik, 1983). Furthermore, platelets facilitate the adhesion of tumour cells to the vascular endothelium (Rickles *et al*., 2001), and release a number of growth factors that can be used by tumour cells for growth (Honn & Tang, 1992; Honn *et al*., 1992b).

What molecular mechanisms control the aggregating ability of cancer cells? Over the past years both TCIPA-stimulator and -inhibitor factors have been described. Cancer cells have the ability to stimulate the release of platelet granules leading to the liberation of potent proaggregatory agents. Adenosine diphosphate (ADP), an element of platelet dense granules is one of such agents. ADP contributes to TCIPA induced by SKNMC neuroblastoma (Bastida *et al*., 1986b), small-cell lung (Heinmoller *et al*., 1996), melanoma M1Do., M3Da., M4Be (Boukerche *et al*., 1994), breast carcinoma MCF7 (Alonso-Escolano *et al*., 2004) and fibroblastoma HT-1080 (Jurasz *et al*., 2001a) cells. It has been shown that ADP released during MCF-7-induced TCIPA aggregates platelets *via* activation of the $P2Y_{12}$ purinergic receptor (Alonso-Escolano *et al*., 2004).

Thromboxane A_2, a potent platelet-aggregatory eicosanoid (Needleman *et al*., 1976), is also generated during TCIPA and stimulates platelet aggregation induced by murine and human tumour cell lines (Grignani *et al*., 1986; 1989; Pacchiarini *et al*., 1991; Tzanakakis *et al*., 2002; de Leval *et al*., 2003) most likely *via* activation of thromboxane receptors on platelets. In addition to TXA_2, platelet activation with Walker 256 carcinosarcoma cells leads to upregulation of the arachidonic acid 12-lipoxygenase and the formation of 12-HETE, which stimulates TCIPA (Steinert *et al*., 1993).

TCIPA is also stimulated by serine proteinases including thrombin, cysteine proteinases: cathepsin B and cancer procoagulant (EC 3.4.22.26), and matrix metalloproteinases (MMPs). Thrombin, a key enzyme in the coagulation cascade, is also the most potent activator of platelet function acting *via* proteinase-activated receptors (PARs) (Kahn *et al*., 1999; Coughlin, 2000; Chung *et al*., 2002). Human glioblastoma U87MG (Bastida *et al*., 1986b), neuroblastoma (Esumi *et al*., 1987) and pancreatic cancer (Heinmoller *et al*., 1995) cells have the ability to generate thrombin, thus increasing TCIPA. Cathepsin B and cancer procoagulant induce aggregation when released from cancer cells (Honn *et al*., 1982; Falanga & Gordon, 1985; Donati *et al*., 1986), an effect that may be related to the generation of oxygen-derived free radicals by platelets (Olas *et al*., 2000).

Matrix metalloproteinases are a family of zinc-dependent endopeptidases that are also involved in the regulation of platelet function (Jurasz *et al*., 2002). We have recently shown that the release of MMP-2 both from platelets, as well as from cancer cells, is involved in TCIPA induced by HT-1080 and MCF7 cells (Jurasz *et al*., 2001a, b; Alonso-Escolano *et al*., 2004). The aggregating effects of MMP-2 are dependent upon the activation of proMMP-2 to MMP-2 by MMP-14 (Alonso-Escolano *et al*., 2004). Interestingly, increased aggregability of platelets collected from patients with metastatic prostate cancer can be related to enhanced generation of MMP-2 (Jurasz *et al*., 2003b).

There is strong evidence implicating adhesion receptors: GPIb-IX-V, GPIIb/IIIa and P-selectin in TCIPA (Oleksowicz & Dutcher, 1995). Indeed, GPIb-IX-V expression is observed on the surface of platelets and MCF7 cells during TCIPA (Oleksowicz *et al*., 1995; Jurasz *et al*., 2001b; Alonso-Escolano *et al*., 2004). Furthermore, purified von Willebrand factor potentiates TCIPA induced by HT-1080 cells (Jurasz *et al*., 2001b), while inhibition of GPIb-IX-V or von Willebrand factor function with blocking antibodies reduced platelet–cancer cell interactions (Karpatkin *et al*., 1988; Clezardin *et al*., 1993; Oleksowicz *et al*., 1995). Numerous contributions point to a crucial role of the integrin receptor, GPIIb/IIIa, in TCIPA-induced by cancer cells of various origin both *in vitro* and *in vivo* (Chopra *et al*., 1988; Grossi *et al*., 1988; Karpatkin *et al*., 1988; Boukerche *et al*., 1989a, b; Honn *et al*., 1992a; Clezardin *et al*., 1993; Oleksowicz *et al*., 1995; Cohen *et al*., 2000; Trikha *et al*., 2002; Amirkhosravi *et al*., 2003; Alonso-Escolano *et al*., 2004). Another integrin receptor $\alpha_v\beta_3$, which is expressed in low amounts on platelets, but is abundant on cancer cells, may play a role in TCIPA connecting tumour cells to platelets using plasma proteins such as fibrinogen (Felding-Habermann *et al*., 2001). Finally, P-selectin and its association with mucin is likely to mediate TCIPA in a variety of mucin-producing cancers (Stone & Wagner, 1993; Pottratz *et al*., 1996; Iwamura *et al*., 1997; Kim *et al*., 1998; 1999; Varki & Varki, 2001; Wahrenbrock *et al*., 2003).

Potent platelet-regulatory agents such as prostacyclin and nitric oxide (NO) have been shown to control TCIPA. Prostacyclin is the most potent known inhibitor of platelet aggregation (Moncada *et al*., 1976) and the administration of this compound leads to inhibition of TCIPA (Honn *et al*., 1981a, b; 1982; Honn & Meyer, 1981; Lerner *et al*., 1983; Menter *et al*., 1984; 1987a, b; Longenecker *et al*., 1989; Radomski *et al*., 1991; Schneider *et al*., 1991; Schirner & Schneider, 1992; Jurasz *et al*., 2001b). Furthermore, the balance between endogenous prostacyclin and TXA_2 may affect the fate of platelet–cancer cell aggregates in blood (Honn & Meyer, 1981; Honn *et al*., 1981a, b). In order to control haemostasis prostacyclin interacts with other regulatory mediators including NO. In the vascular system, NO is mostly generated by the endothelial cells, platelets and leukocytes (Jurasz *et al*., 2000). Interestingly, some human adenocarcinoma cells (SW480 and SW620) have the ability to generate NO and this generation attenuates TCIPA (Radomski *et al*., 1991; Jenkins *et al*., 1994), an effect potentiated by prostacyclin (Radomski *et al*., 1991). How the platelet-inhibitory effects of NO translate into regulation of cancer growth, invasion, and metastasis is uncertain. This is not unexpected considering the complex and multifaceted actions of NO including regulation of vasodilatation (Palmer *et al*., 1988), cell adhesion (Radomski *et al*., 1987), and its effects on cellular growth, proliferation, and cell migration (Lepoivre *et al*., 1991; Goligorsky *et al*., 1999; Schini-Kerth, 1999).

The interactions between cancer cells and platelets during TCIPA are reciprocal in their nature. This concept is best illustrated when the network of platelet–cancer cell adhesion molecules is considered. The expression of platelet GPIb-IX-V, GPIIb/IIIa and P-selectin on the tight interjunction between platelet and cancer cells is crucial for TCIPA. Interestingly, not only cancer cells have the ability to stimulate the platelet receptor expression, but also platelets themselves upregulate GPIb-IX- and GPIIb/IIIa on the surface of MCF7 cells (Alonso-Escolano *et al*., 2004).

Thus, cancer cells have a remarkable arsenal of pathways and mechanisms to stimulate TCIPA. However, involvement of these various pathways and mechanisms in tumour progression is likely to vary for different tumour types. For example, the generation of MMPs and the MMP-2-dependent TCIPA is detected in human HT-1080, but to much lesser extent in A549 human adenocarcinoma cells (Jurasz *et al*., 2001a). Furthermore, even in cancer cells deriving from the same tumour (human melanoma cells) or the same patient (colorectal adenocarcinoma cells) there are substantial differences in their ability to aggregate platelets (Radomski *et al*., 1991; Boukerche *et al*., 1994). These differences may contribute to the understanding of clinical observations that patients with cancers of pancreas, brain, ovary, breast, lung and prostate are more likely than others to develop thrombosis (Rickles & Falanga, 2001; Rickles *et al*., 2001; Sutherland *et al*., 2003).

Inhibitors of tumour cell-induced platelet aggregation

The understanding of mechanisms responsible for the formation of platelet–cancer cell aggregates led to testing of various antiplatelet agents as potential inhibitors of TCIPA *in vitro* and *in vivo*. Acetyl salicylic acid (aspirin) is the most commonly used antiplatelet drug that inhibits platelet aggregation *via* inhibition of cyclooxygenase and subsequent TXA_2 generation by platelets (Vane *et al*., 1998). Aspirin is a weak inhibitor of TCIPA *in vitro* (Hamilton *et al*., 1986; Bastida *et al*., 1987; Bradley *et al*., 1997; Jurasz *et al*., 2001a; Alonso-Escolano *et al*., 2004). Early clinical studies found that the treatment with high doses of aspirin ($0.6–1\,g\,day^{-1}$) did not protect patients from metastasis due to colorectal or small-cell lung cancer (Lipton *et al*., 1982; Lebeau *et al*., 1993). However, when used as prophylaxis to decrease the incidence of colorectal adenomas aspirin appears to be effective in reducing the incidence of adenoma, thus decreasing the risk of colorectal cancer (Sandler *et al*., 2003). Furthermore, the regular use of aspirin reduces the risk of hormone receptor-positive breast cancer (Terry *et al*., 2004).

Since aspirin reduces the generation of both pro- and antiaggregatory eicosanoids, pharmacological agents that selectively inhibit thromboxane synthase have been also investigated. While OKY-046, a selective inhibitor of thromboxane synthase, did not reduce osteogenic sarcoma cell-induced TCIPA (Mehta *et al*., 1986), a TXA_2 receptor antagonist, SQ-29,548 and a mixed thromboxane synthase inhibitor/receptor antagonist, BM-567 both effectively reduced TCIPA (Mehta *et al*., 1986; de Leval *et al*., 2003).

Scavenging ADP, which is liberated from platelets and cancer cells, with apyrase decreased TCIPA (Grignani *et al*., 1989; Boukerche *et al*., 1994; Jurasz *et al*., 2001a; Alonso-Escolano *et al*., 2004). Similar effects to apyrase could be demonstrated using selective inhibitors of the $P2Y_{12}$ receptor such as 2-methylthio-AMP (Alonso-Escolano *et al*., 2004), and a clinically relevant P2Y antagonist, ticlopidine (Bando *et al*., 1984; Bastida *et al*., 1986a).

Apyrase collaborates with phenanthroline, an inhibitor of MMPs to inhibit MCF7-induced TCIPA (Alonso-Escolano *et al*., 2004). Selective inhibition of MMPs with blocking anti-MMP-2 antibodies or tissue inhibitor of metalloproteinase-4 (TIMP-4) also decreased TCIPA induced by MCF7 and HT-1080 cells (Jurasz *et al*., 2001a; Radomski *et al*., 2002; Alonso-Escolano *et al*., 2004). Of note, pharmacological inhibitors of MMPs have been used in a number of clinical trials to delay the progress of advanced malignancies. The results of these trials to date have been largely disappointing, as no significant benefits has been reported during clinical administration of MMP inhibitors (Overall & Lopez-Otin, 2002).

The antagonists of GPIIb/IIIa receptor are the most effective known inhibitors of TCIPA. Karpatkin *et al*. (1988) first indicated that the drugs belonging to this group hold a potential to reduce TCIPA). Both intravenous (e.g. Abciximab) (Cohen *et al*., 2000) and oral (e.g. XV454) (Amirkhosravi *et al*., 2003) antagonists are potent inhibitors of TCIPA. In addition to inhibition of TCIPA, these compounds may reduce the adhesion of tumour cells to the endothelium and angiogenesis. Some of these effects could result from inhibition of the biological activity of $\alpha_v\beta_3$ (Cohen *et al*., 2000; Bakewell *et al*., 2003). The angiogenesis-inhibitory effects of GPIIb/IIIa antagonists are highly desirable given a substantial contribution of platelets to this process (Pinedo *et al*., 1998; Maragoudakis *et al*., 2000; Pinedo & Slamon, 2000; Salgado *et al*., 2001; Jurasz *et al*., 2003a; Manegold *et al*., 2003).

Antiplatelet drugs, in addition to inhibiting cancer cell–platelet interactions, may also block tumour progression independent of their effects on platelets. Two studies based on the antiplatelet hypothesis investigated the effect of the phosphodiesterase inhibitor Mopidamol (RA-233) in non-small cell lung cancer (Zacharski *et al*., 1988; Blaha *et al*., 1989). While these studies showed Mopidamol significantly increased patient survival, the authors hypothesized that the effects may have been due to Mopidamol's direct antineoplastic properties.

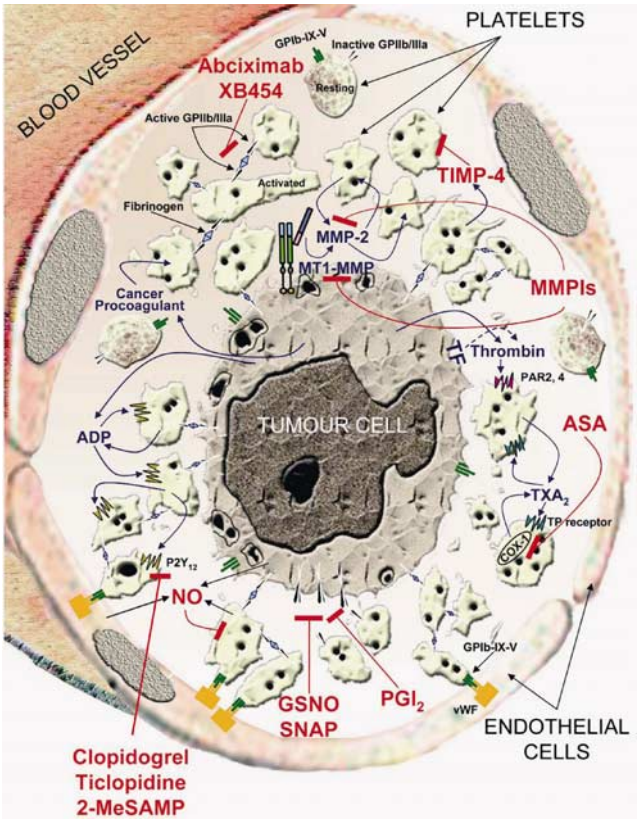

Figure 1 Major mechanisms and pharmacology of TCIPA depicting the interactions between tumour cells, platelets, and endothelial cells. Mediators and antagonists of TCIPA are shown in blue and red, respectively. ASA, acetyl salicylic acid; COX-1, cyclooxygenase-1; GSNO, *S*-nitrosoglutathione, MMPIs, matrix metalloproteinase inhibitors; 2-MeSAMP, 2-methylthio-AMP; PGI_2, prostacyclin; SNAP, S-nitroso-*N*-acetylpenicillamine; TF, tissue factor, vWF, von Willebrand factor.

Summary and conclusions

The multiplicity of molecular mechanisms that can be utilized by cancer cells to aggregate platelets (Figure 1) makes attempts of pharmacological inhibition of TCIPA rather challenging and uncertain. In spite of the abundant preclinical data and some positive clinical trials, the therapeutic strategy of antiplatelet drugs in cancer has not received significant attention from the oncology community. This may be due to the fact that antiplatelet agents are not cytotoxic, and therefore not considered as antitumour drugs (Zacharski, 2002). This lack of attention may be also due to mixed results of clinical trials, and the medical community's tendency to abandon therapeutic strategies where clinical failures have resulted, even in light of some clinical successes. Therefore, data from carefully designed controlled clinical trials will be required for cancer treatment based on this paradigm to become routine. However, since the molecular rationale for this strategy is compelling, and highly effective antiplatelet drugs such as fibrinogen receptor antagonists are clinically available, larger controlled investigations with antiplatelet drugs in cancer are warranted (Hejna *et al*., 1999; Bakewell *et al*., 2003).

The most challenging problem of the use of antiplatelet drugs in cancer is the lack of selectivity. Indeed, the currently available antiplatelet drugs affect both haemostasis and cancer-induced thrombosis. However, we envision that recent advancements in nanotechnology research may facilitate the development of selective drug delivery systems for targeting TCIPA. Finally, patient-specific molecular mechanisms utilized by cancer cells to aggregate platelets will need to be identified in order for the rational choice of antiplatelet drugs in clinical trials.

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