The traditional view of the role of proteases in tumor growth, progression and metastasis has significantly changed. Apart from their contribution to cancer progression, it is evident that a subclass of proteases, such as thrombin, serves as signal molecules controlling cell functions through the protease-activated receptors (PARs). Among the four types of PAR (PAR1-4; cloned and named in order of their discovery), PAR1, PAR3 and PAR4 are activated by thrombin, unlike PAR2, which is activated by trypsin-like serine proteases. Thrombin has been proven to be a significant factor in both the behavior of cancer and in its involvement in hemostasis and blood coagulation. Thrombin is a key supporter of various cellular effects relevant to tumor growth and metastasis, as well as a potent activator of angiogenesis, which is essential for the growth and development of all solid tumor types. This review presents an overview of the role of PAR-mediated thrombin in angiogenesis and cancer, focusing on the ability of PAR1- and PAR4-mediated thrombin to affect tumorigenesis and angiogenesis.

Abstract. The traditional view of the role of proteases in tumor growth, progression and metastasis has significantly changed. Apart from their contribution to cancer progression, it is evident that a subclass of proteases, such as thrombin, serves as signal molecules controlling cell functions through the protease-activated receptors (PARs). Among the four types of PAR (PAR1-4; cloned and named in order of their discovery), PAR1, PAR3 and PAR4 are activated by thrombin, unlike PAR2, which is activated by trypsin-like serine proteases. Thrombin has been proven to be a significant factor in both the behavior of cancer and in its involvement in hemostasis and blood coagulation. Thrombin is a key supporter of various cellular effects relevant to tumor growth and metastasis, as well as a potent activator of angiogenesis, which is essential for the growth and development of all solid tumor types. This review presents an overview of the role of PAR-mediated thrombin in angiogenesis and cancer, focusing on the ability of PAR1- and PAR4-mediated thrombin to affect tumorigenesis and angiogenesis.

Contents

1. Introduction
2. Thrombin level in cancer and PAR activation
3. Thrombin and PAR in angiogenesis
4. Thrombin and PAR in tumorigenesis and metastasis
5. Therapeutic implications in cancer
6. Conclusions

1. Introduction

The G-protein-coupled receptor (GPCR) superfamily comprises the largest and most functionally diverse group of signaling molecules. These receptors play essential roles in the normal regulation of the majority of biological processes. They are also of great significance in human diseases, such as cancer. GPCRs are able to interact with a variety of agonists, such as peptides, lipids and ions. Proteases are one of the most noteworthy agonists of GPCRs.

Proteases have previously been associated with tumor progression due to their ability to degrade extracellular matrices, facilitating tumor cell invasion and metastasis (1). However, studies have shown that these enzymes target diverse substrates and promote tumor evolution (2), a fact that significantly altered the traditional view of the role of proteases in tumor growth and progression. It is well known that a subclass of proteases serves as signal molecules controlling cell functions through specific GPCRs, the protease-activated receptors (PARs) (3,4). The PARs are activated by low concentrations of certain extracellular serine proteases. Four types of PAR (PAR1-4) have been cloned and named in order of their discovery. These PARs share the same basic mechanism of activation in that proteases cleave at a specific site within the extracellular N-terminus to expose a new N-terminal tethered ligand domain, which binds to and activates the cleaved receptor. PAR1, PAR3 and PAR4 are activated by thrombin, one of the important extracellular serine proteases (5,6). On the other hand, PAR2 is activated by trypsin-like serine proteases, including trypsin, trypate and coagulation proteases upstream of thrombin, tissue factors (TFs) VIIa and Xa, but not by thrombin (4,7-12).

Thrombin has been proven to be crucial in the behavior of cancer and in its involvement in hemostasis and blood coagulation. Thrombin is a key supporter of various cellular effects relevant to tumor growth and metastasis as well as a potent
activator of angiogenesis, which is essential for the growth and development of all solid tumor types. Thrombin actions in cancer are PAR-mediated.

This review provides an overview of the role of PAR-mediated thrombin actions in cancer, focusing on the involvement of PAR1- and PAR4-mediated thrombin in tumorigenesis and angiogenesis.

2. Thrombin level in cancer and PAR activation

Thrombin generated in the circulation during activation of the coagulation cascade has multiple cellular effects, including the induction of cell proliferation and motility, enhancement of vascular permeability, deposition of matrix fibrin, promotion of tumor cell seeding, adhesion to endothelium and extracellular matrix, induction of platelet aggregation, and enhancement of the metastatic capacity of tumors (13,14). A common feature in cancer patients is the high level of thrombin formation in tumor cells. It has been shown that numerous tumor cell types express the transmembrane protein tissue factor, which, when exposed to circulating factor VII, activates factor X, leading to the generation of thrombin (15). Thrombin generation is possibly a direct result of the over-activation of the coagulation system (hypercoagulability), a widely described abnormality in various cancer patients (16).

Thrombin activates PAR1, PAR3 and PAR4. Thrombin activates PAR1 in two stages (9). Firstly, it binds to PAR1 on either side of the cleavage site. Secondly, it cleaves PAR1 between Arg41 and Ser42 to expose a new N-terminal tethered ligand domain, SFLLRN. The tethered ligand interacts with domains in extracellular loop 2, which presumably alters the conformation of the receptor to permit coupling to G-proteins. PAR3 also contains the thrombin binding sites, whereas PAR4 lacks thrombin binding sites and only responds to higher concentrations of thrombin (5,11). The differences in the mechanism of activation mentioned above exhibit functional consequences in tumorigenesis and angiogenesis.

3. Thrombin and PARs in angiogenesis

Action of PAR-mediated thrombin on endothelial cells.

Although thrombin is best known for its direct role in clot formation via platelet activation and fibrin deposition, a number of the effects of thrombin in cancer may be mediated by promoting angiogenesis in vivo (17-19). Numerous cellular effects of thrombin on endothelial cells contribute to the angiogenic action of thrombin (Table I) (17-30).

Angiogenesis involves the activation and invasion of the endothelial cells through their basement membrane and migration to distal sites. Studies have demonstrated that thrombin contributes to each of these events (18,19,23-25). This cellular action of thrombin on endothelial cell adhesion may indicate a significant role in the activation of the normally quiescent endothelial cells in the initiation of the angiogenic cascade. A key event in early angiogenesis is the local dissolution of the basement membrane of the parent vessel. Endothelial cells need to overcome the barrier of their anchorage to basement membrane components in order to migrate to distal sites, proliferate and form the lumen of the new vessel. Exposure of endothelial cells to thrombin causes a time- and dose-dependent decrease in the attachment of these cells to basement membrane components, with a concomitant increase in matrix metalloproteinase 2 (MMP-2) activation (24,25). This decrease not only allows for the migration of endothelial cells, but releases other angiogenic factors that are sequestered in the extracellular matrix.

Integrin \(\alpha_v\beta_3\) was identified as a marker of the angiogenic phenotype of endothelial cells in vascular tissue (31). Antibodies or peptide antagonists of this integrin inhibited angiogenesis induced by basic fibroblast growth factor in the rabbit cornea model (26). Furthermore, integrin \(\alpha_v\beta_3\), antagonists inhibit tumor-induced angiogenesis by inducing apoptosis in angiogenic blood vessels without affecting mature vessels, which express minimal \(\alpha_v\beta_3\). Endothelial cells attach to thrombin via the angiogenic integrin \(\alpha_v\beta_3\), which is up-regulated by thrombin (19,25). This attachment provides endothelial cells with survival signals during their anchorage-independent migration (19). More importantly, both integrin \(\alpha_v\beta_3\) and MMP-2 functionally coexist on the surface of angiogenic capillaries (26).

Thrombin also has chemotactic and apoptotic effects on endothelial cells in that it up-regulates the expression of the vascular endothelial growth factor (VEGF) receptors (KDR and Flt1) and synergizes with the key angiogenic factor VEGF in endothelial cell proliferation (27). It has been shown that 8-12 h after exposure of endothelial cells to thrombin, cells are sensitized to the action of VEGF. The mitogenic activity is increased by more than 100% over the level expected from the additive effects of thrombin and VEGF alone. The thrombin-treated cells respond to VEGF-induced DNA synthesis in a synergistic manner (27). This synergistic effect

<table>
<thead>
<tr>
<th>Effects of thrombin on ECs</th>
<th>PAR-mediated</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in the attachment of ECs to BMC</td>
<td>PAR1-, PAR3- and PAR4-mediated</td>
<td>17, 18-22</td>
</tr>
<tr>
<td>Increase in MMP-2 activation</td>
<td></td>
<td>23, 24</td>
</tr>
<tr>
<td>Up-regulation of integrin (\alpha_v\beta_3)</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Chemotactic and apoptotic effects on ECs</td>
<td></td>
<td>19, 25, 26</td>
</tr>
<tr>
<td>Up-regulation of VEGF receptors (KDR and Flt1)</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Up-regulation of VEGF</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Synergy with VEGF in EC proliferation</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Vascular smooth muscle cell migration</td>
<td></td>
<td>29, 30</td>
</tr>
</tbody>
</table>

ECs, endothelial cells; BMC, basement membrane components; MMP-2, matrix metalloproteinase 2; VEGF, vascular endothelial growth factor.
Table II. Dual regulation of platelets on angiogenesis.

<table>
<thead>
<tr>
<th>Dual regulation of platelets on angiogenesis</th>
<th>PAR-mediated</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-angiogenic regulation of platelets by releasing angiogenic promoters:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>PAR1-mediated</td>
<td>42,45,48,51-58</td>
</tr>
<tr>
<td>bFGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMPs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-angiogenic regulation of platelets by releasing angiogenic inhibitors:</td>
<td>PAR4-mediated</td>
<td>50</td>
</tr>
<tr>
<td>Endostatin</td>
<td></td>
<td>48,59,60</td>
</tr>
<tr>
<td>Platelet factor-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombospondin-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-macroglobulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiostatin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; PDGF, platelet derived growth factor; MMPs, matrix metalloproteinases.

of thrombin with VEGF can be explained by the finding that thrombin increases the level of VEGF receptors KDR and Fli-t1 as mentioned above.

The PAR family members, PAR1, PAR2, PAR3 and PAR4, are expressed in arterial and/or venous endothelial cells (20,22,32-34). Endothelial PARs serve as sensors of extracellular proteases and transmit signals after cleavage by proteases such as thrombin (35,36). Previous studies indicated that coagulation factors upstream and downstream of thrombin mediate the activation of PAR1 in endothelial cells (35-37). Thrombin activation of PAR1 generates cytoskeletal rearrangements in endothelial cells and induces cell contraction and rounding (38,39). Endothelial cell contraction destabilizes cell-cell contacts, causing a subsequent increase in vascular permeability that facilitates the passage of molecules and cells from the blood into subendothelial compartments. Activation of PAR1 in the vascular endothelium also leads to increased surface expression of the adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, P-selectin and E-selectin (40).

Action of PAR-mediated thrombin on platelets. The process of postnatal angiogenesis is regulated by a continuous interplay of stimulators and inhibitors of angiogenesis, and their imbalance contributes to numerous inflammatory, malignant, ischemic and immune disorders (41). A renewed interest in the overlap between angiogenesis and platelets has been observed (42) with findings of various clinical trials showing that anticoagulation improves cancer survival (43,44) beyond the benefit derived from the treatment of deep vein thrombosis alone. Platelets act as the initial responder to vascular change and provide a flexible delivery system for angiogenesis-related molecules (45-48).

It is known that platelets stimulate endothelial cells in culture and promote the assembly of capillary-like structures in vitro (49). Platelets may modulate angiogenesis by releasing promoters, such as VEGF, basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and matrix metalloproteinases (MMPs) (Table II) (42,45,48,50-58). Platelets comprise a wide range of angiogenesis inhibitors including endostatin, platelet factor-4, thrombospondin-1, 2-macroglobulin, plasminogen activator inhibitor-1 and angiostatin (Table II) (48,59,60). Although platelets contain three types of secretory granules (α-granules, dense granules and lysosomes), most angiogenic regulatory proteins have been localized to α-granules. α-granules comprise proteins that enhance the adhesive process, promote cell-cell interactions and stimulate vascular repair. By adhering to the endothelium of injured organs and tissues and then secreting the contents of their α-granules, platelets may be capable of depositing high concentrations of angiogenesis regulatory proteins in a localized manner (50).

Platelets are regulated through numerous agonist-induced signaling pathways, the most potent of which is thrombin (61,62). Human platelets express two functional thrombin receptors, PAR1 and PAR4 (63-65). Thrombin acts through PAR1 and PAR4 on human platelets to signal activation responses, such as calcium mobilization, release of procoagulant molecules (e.g., P-selectin) from α-granules, release of small molecules (e.g., ADP) from dense granules, activation of glycoprotein IIbIIIa/integrin αIIbβ3, (GPIIbIIIa) and aggregation (65-72). Thrombin activates PAR1 at concentrations 10-fold less than PAR4, but activation of PAR4 provides a longer stimulus (61,73).

Numerous experimental data and clinical investigations have suggested that platelets are major regulators of angiogenesis. However, since platelets contain both pro- and anti-angiogenic regulatory proteins and because it has been assumed that the contents of α-granules are homogeneous, it is unclear how platelets either stimulate or inhibit angiogenesis. Italiano et al. (50) provided new details about the organization of angiogenesis regulatory proteins in the α-granules of platelets and addressed the mechanism of how the selective release of these granules leads to the regulation of angiogenesis. Using double immunofluorescence and immunoelectron microscopy, these authors showed that pro- and anti-angiogenic proteins are divided into distinct subpopulations of α-granules in platelets and megakaryocytes. The double immunofluorescence labeling of VEGF and endostatin, or that for thrombospondin-1 and bFGF, confirms the segregation of stimulators and inhibitors into separate and distinct α-granules. These observations motivated the hypothesis that distinct populations of α-granules undergo selective release. Furthermore, the treatment of human platelets with a selective PAR4 agonist (AYPGKF-NH2) resulted in the release of endostatin-containing, but not VEGF-containing granules, whereas the selective PAR1 agonist (TFLLR-NH2) released VEGF, but not endostatin-containing granules. Results of this
study (50) demonstrated the separate packaging of angiogenesis regulators into pharmacologically and morphologically distinct populations of \( \alpha \)-granules in platelets and may provide a mechanism by which platelets locally stimulate or inhibit angiogenesis. Tumors may hijack the angiogenic properties of platelets to generate new blood vessel growth by manipulating the PARs on platelets and triggering the selective release of predominantly proangiogenic factors.

4. Thrombin and PARs in tumorigenesis and metastasis

Action of PAR-mediated thrombin in tumorigenesis. Thrombin markedly increases the growth potential of tumor cells (Table III) (74-81), although these effects may be partially attributed to its pro-angiogenic effects (27,82). By mobilizing adhesion molecules, such as the \( \alpha_\text{IIb} \beta_3 \) integrin (83-85), P-selectin (86,87) and CD40 ligand (88) to the cell surface, thrombin enhances adhesion between tumor cells, platelets, endothelial cells and the extracellular matrix, and contributes to tumor progression. Thrombin also triggers the release of growth factors (89), chemokines and extracellular proteins (90) that promote the proliferation and migration of tumor cells.

The microenvironment of tumors is replete with thrombin, which activates PARs, and tumor cells, which also express PARs. Malignant cells secrete thrombin, which affects proliferation and mediates metastatic processes, such as cellular invasion, extracellular matrix degradation, angiogenesis and tissue remodeling. In the setting of cancer, the ability of thrombin to act via PARs was highlighted by the demonstration of PAR expression in carcinosarcoma (91). Additionally, mounting evidence showed that the PAR family is involved in neoplasia (92). In particular, PAR1 is expressed by a wide range of tumor cells (91,93-96). The expression of PAR1 has been correlated with the malignant phenotype. For PAR1, a role in the progression of epithelial tumors, including breast (75,82,94,97,98), colon (76,99), kidney (100), pulmonary tumor (101), melanoma (102) and hepatocellular carcinoma (80,103) has been shown.

The effects of thrombin in human colon cancer cells have been found to be mediated by functional PAR4. Firstly, the
PAR4 agonist AP4 mimics the effects of thrombin on cell proliferation. However, AP4 does not activate other PARs. Secondly, the challenge of CHO-PAR4-expressing cells with AP4 has the same impact on calcium transients as that in HT-29 cells. Thirdly, no effect on calcium transients is noted following the challenge of HT-29 cells with reverse peptide.

AP4 was capable of promoting colon cancer cell proliferation since, at maximally active concentrations, its effect exhibited up to a 250% increase in the cell number in HT-29 cells. PAR4 should thus be regarded as a crucial receptor by which thrombin modulates colon carcinogenesis (104).

Action of PAR-mediated thrombin in tumor metastasis. Tumor cell metastasis or the dissemination of a tumor from its original site to distant organs and tissues is an inherently inefficient process. The ability of tumor cells to activate the coagulation system and to generate thrombin has been shown to enhance metastatic efficiency (105-108), while anticoagulant therapies interfere with metastatic disease in animal models and in humans (109). The prometastatic activity of thrombin in cancer has been well demonstrated (Table IV) (74,75,82,84,97,98,110-113). The principal thrombin receptor, PAR1, has been implicated in the promotion of these effects (Table IV).

PAR1 expression is correlated with metastatic potential. In human breast cancer, PAR1 expression is associated with tumor progression (82), and in prostate cancer it plays a role in bone metastasis (114). Metastatic human melanoma cell lines express PAR1 (102,110). The overexpression of PAR1 in murine and human melanoma cells results in enhanced metastasis in mice (98,115). The overexpression of PAR1 also increases matrigel invasion by melanoma cells (112) and thrombin stimulates the motility of colon carcinoma cells in a PAR1-dependent manner (76,78). Pre-treatment of tumor cells with PAR1 agonist peptides alters their adhesive behavior and increases pulmonary metastasis (98). Thrombin-dependent PAR1 signaling induces the proliferation of metastatic tumor cells (116) and can be anti-apoptotic (117). PAR1 enhances the \( \alpha_v\beta_5 \) integrin-dependent migration of tumor cells (118). PAR1 has also been proposed to play a role in the pathological invasion processes of breast cancer (82,97).

The prometastatic effects of thrombin on tumor cells may involve the receptor cross-activation of PAR2, due to the fact that the metastasis was enhanced by PAR2 stimulation (111). Although the precise mechanism of PAR2 signaling in metastasis remains to be determined, it is known that the tethered ligand of PAR1 activates PAR2. PAR2 may thus be activated by thrombin-cleaved PAR1, and PAR2 may act as a relevant receptor for thrombin signaling under certain conditions (119).

5. Therapeutic implications in cancer

The angiogenic and tumor-promoting effects of thrombin provide the basis for the development of thrombin receptor antagonists for therapeutic application in cancer. A number
of promising targets may be utilized for drug discovery for cancer therapeutics within the clotting cascade. Therapeutic approaches to down-regulating thrombin generation in cancer may accomplish three goals: anticoagulation, prevention of angiogenesis and prevention of tumor growth and metastasis.

Thrombin directly affects signaling pathways that mediate cell functions and clot formation, which provide a growth medium for tumor cells. Therefore, anticoagulant drugs may prove efficacious in cancer treatment as they are capable of reducing the hypercoagulability of cancer. Thrombin-targeted anticoagulant strategies designed to affect both the prothrombotic properties of tumors and their growth and metastatic potential, have been evaluated in a number of pre-clinical and clinical studies (120-122). However, studies providing convincing evidence that this approach predictably improves survival in cancer are limited (43,44).

Since it is believed that all tumors require angiogenesis for tumor growth and metastasis, targeting tumor vasculature with anti-angiogenic agents has developed into a novel strategy for treating a number of solid tumors (123,124). Anti-angiogenic agents generally elicit few toxic side effects in contrast to standard chemotherapeutic agents. Nevertheless, patients treated with both anti-angiogenic agents and standard chemotherapy resulted in an unexpected high incidence of both arterial and venous thrombosis, as reported in a number of clinical trials (123,125). This serious complication has been observed with various promising anti-angiogenic agents, including VEGF Trap (124,125). It is plausible that synergistic vascular toxicity occurs between anti-angiogenic agents and chemotherapy drugs since virtually all chemotherapeutic agents injected intravenously stimulated increased thrombin generation (126). Therefore, adding thrombin-targeted anticoagulants to combination drug regimens, including agents that interact with the endothelium, may aid in the prevention of some of these thrombotic complications by blocking thrombin generation (126,127). Further stimulation for the addition of anticoagulants to cancer treatment regimens is evident in recent experimental studies in which non-anticoagulant properties of anticoagulant drugs have been exploited to reduce angiogenesis, tumor growth and metastasis (128-131).

Combination regimens of standard chemotherapeutics with anticoagulants may provide added benefit for control of tumor progression and simultaneously reduce the risks for serious thrombotic complications. However, such a hypothesis should be confirmed by prospective randomized controlled clinical trials of anticoagulant drugs in cancer.

Inhibitors of thrombin have achieved success in anticoagulant therapy, but are also accompanied with the risk of bleeding (132,133). PARs themselves were considered to be attractive targets for therapeutic drug development. Efforts to develop receptor inhibitors as compared to targeting thrombin are currently regarded as a priority. As outlined in Table V (134-152), substantial success has been achieved in the development of PAR1 and PAR4 antagonists.

PAR antagonists act by blocking the interaction of the newly exposed tethered ligand with binding sites on the extracellular surface of the receptor, but do not inhibit thrombin binding or receptor cleavage. Small molecule PAR1 antagonists have been generated based on the structure of the peptide ligand for PAR1 (4). Bradykinin-derived blocking peptides appear to directly bind and suppress PAR1 activation and do not act as thrombin inhibitors (137). However, a number of these molecules lack PAR1 selectivity due to structural similarities to activating peptides of other PARs. More selective and potent non-peptide PAR1 antagonists for both experimental studies and pharmaceutical use in humans are also currently available (7,137,139-143). In addition to increased PAR1 selectivity, these compounds exhibit relatively potent inhibitory actions against both thrombin and agonist/peptide-stimulated responses. The orally active PAR1 antagonist developed by Schering (SCH-205831), which suppresses PAR1 by competitively inhibiting the TL-binding site (143), has been found to be effective as an antithrombotic agent in humans. A number of other PAR1 antagonists and monoclonal antibodies generated against the cleavage site of PAR1 have also been used to block the activation of PAR1, but their use is limited by relatively low efficacies (134,146, 153-155). The development of effective PAR1 antagonists is in the early stages. However, further description and classification of the recently developed compounds is likely to yield crucial data towards generating novel effective antagonists for PAR1, as well as for other PARs.

PAR4 antagonism has also been shown using the peptide trans-cinnamoyl-YPGKF-NH₂, in human platelets (148), although its use in vivo was limited to its non-PAR actions (156). A novel approach to receptor inhibition, through targeting the receptor intracellular loops with palmitoylated membrane-penetrating peptides termed pepducins, has succeeded in developing a relatively high potency PAR4 antagonist (135,150,157). Pepducin, P4pal-10, has been proven to be of use in blocking PAR4 activation both in vivo and in vitro (135,157), although it is not completely selective for PAR4 (156).

6. Conclusions

Evidence of PAR-mediated thrombin functions in angiogenesis, tumorigenesis and metastasis is well established, as mentioned above. PAR-mediated thrombin exerts its effects in cancer indirectly by promoting angiogenesis, which is essential for the growth and development of all solid tumor types, and directly by promoting tumor growth and metastasis. The key objective of investigating the role of PAR-mediated thrombin in cancer is to develop thrombin-targeted drugs and PAR antagonists for therapeutic application in cancer treatment. Thrombin-targeted anticoagulant strategies designed to affect both the prothrombotic properties of tumors and their growth and metastatic potential have been evaluated in a number of pre-clinical and clinical studies. However, studies providing evidence that this approach may predictably improve survival in cancer are limited. Therapeutic approaches that target PARs themselves were considered to be attractive targets for therapeutic drug development. The development of effective PAR antagonists, however, remains in the early stages.

Acknowledgements

This study was supported by the State Key Basic Research and Development Program of China (973 Program, Grant No. 2009CB521704), the National High-tech Research and
Development Program of China (863 Program, Grant No. 2006AA02A245), the National Natural Science Foundation of China (Grant No. 30271450 and 30672365) and the Zhejiang Provincial Science and Technology Project (Grant No. 2009C31021).

References


57. Carson HF and Sharpe RJ: Inhibition of angiogenesis by recom


60. Chiang HS, Yang RS and Huang TF: Thrombin enhances the adhesion and migration of human colon adenocarcinoma cells via increased beta 3-integrin expression on the tumour cell surface and their inhibition by the snake venom peptide, rhodos


