Angiogenesis in cancer*
Basic mechanisms and therapeutic advances

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Summary
Etiological concepts on cancer development, malignant growth and tumour propagation have undergone a revolutionary development during recent years: Among other aspects, the discovery of angiogenesis – the growth of new blood vessels from pre-existing vasculature – as a key element in the pathogenesis of malignancy has opened an abundance of biologic insights and subsequent therapeutic options, which have led to improved prognosis in many cancers including those originating from colon, lung, breast and kidney. Thereby, targeting the major pro-angiogenic stimulus vascular endothelial growth factor (VEGF) became the focus for therapeutic interventions. However, the use of VEGF-targeting drugs has been shown to be of limited efficacy, which might lie in the fact that tumor angiogenesis is mediated by a variety of different subcellular systems.

This review focuses on the basic mechanisms involved in angiogenesis, which potentially represent novel targets for pharmacological agents in the treatment of malignancies.

Schlüsselwörter
Angiogenese, Tumorerkrankung, Endothelzellen

Zusammenfassung

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The development of new blood vessels from preexisting vasculature, the so called angiogenesis, is a tightly regulated process, which is induced when the net balance of pro- and anti-angiogenic molecules is tipped in favour of angiogenesis, resulting in the ‘angiogenic switch’ (1, 2). During tumour growth angiogenesis is induced by a variety of stimuli. Thereby, rapid cell proliferation causes hypoxia as oxygen diffusion is limited by tissue growth. Hypoxia is an important stimulus of tumour vessel growth (3), which leads to stabilization of hypoxia-inducible factor-1α (HIF-1α) and HIF-1 target genes. Among them, many pro-angiogenic growth factors /-receptors, e. g. VEGF-A, fibroblast growth factor-3 (FGF-3), hepatocyte growth factor (HGF), Tie-2,
transcription factors, e. g. annexin V, heat-shock factor, insulin-like growth factor (IGF) binding protein-1, –2, –3, JUN,
cell adhesion molecules (integrin adhesion receptors), and
extracellular matrix proteins and proteases, e. g. urokinase receptor, uPAR; matrix metalloproteinases, MMPs; plasminogen activator inhibitor-1, PAI-1 are upregulated (4).

VEGF-A is the major angiogenic growth factor and directly stimulates endothelial cells, mainly via its receptor VEGFR-2 (flk-1) or VEGFR-1 (flt-1) (5). While VEGFR-2 elicits an efficient endothelial response by stimulating every single step in angiogenesis, such as endothelial cell survival, cell proliferation, migration and invasion and finally capillary-like tube formation, VEGFR-1 is thought to modulate VEGF binding to VEGFR-2 (6).

VEGF induces also endothelial leakiness, which leads to an enhanced transudation, but also promotes tumour cell-transendothelial migration in vitro. In an experimental setting, these effects could be
reverted by the monoclonal anti-VEGF antibody bevacizumab, suggesting a potential therapeutic role in malignant effusion formation (7).

Since VEGF and VEGFR-2 became the focus of therapeutic intervention in the treatment of malignancies, not only bevacizumab but also the second-generation multi-targeted inhibitor of receptor tyrosine kinases (RTKs) sunitinib, axitinib and sorafenib have led to a significant therapeutic advance in the treatment of cancer (8–11). Although this has been found beneficial for patients with particular tumours – albeit only for a limited duration of time – a substantial fraction of patients with cancer proves to be finally resistant to VEGF-based therapies (12–14). This might be explained in part by recent findings showing that VEGF-targeting drugs may increase invasiveness of tumour cells and metastasis (15, 16). However, clinical evidence shows that in advanced colorectal cancer (mCRC) patients continuation of anti-VEGF treatment beyond progression improves clinical outcome (17).

Nevertheless, the question arises whether concomitantly blockage of other angiogenic growth factors might overcome resistance to anti-VEGF therapy. Contrary to prediction, a recent study revealed that simultaneous targeting of VEGF and EGFR plus chemotherapy in advanced colorectal cancer led to a shorter progression-free survival as anti-VEGF plus chemotherapy alone as shown in the two recent clinical studies PACCE and CAIRO2 (18). Therefore, other and perhaps more downstream targets might be more suitable for effective interference with tumour angiogenesis, thereby blocking tumour growth and metastasis.

The key systems beyond VEGF/VEGFR-2 responsible for angiogenic endothelial cell behaviour are discussed here, which might be novel therapeutic targets to effectively block tumour vessel formation and avoid resistance in cancer.

**Adhesion receptors**

Blood vessel formation is critically dependent on extracellular matrix, whereby integrins are the major adhesion receptors to link matrix proteins with the cytoskeleton. Integrins are a family of heterodimeric transmembrane glycoproteins, consisting of eight β and 18 α subunits that assemble as heterodimers to form 24 distinct integrins (19). Beside its functional role as scaffold proteins, integrins resemble main regulators of tumour angiogenesis by mediating intracellular signalling (20, 21), thereby affecting endothelial cell proliferation, migration and invasion as well as cell survival.

Integrin adhesion receptors do not only mediate endothelial cell attachment to extracellular matrix proteins, but also act as bidirectional transducer molecules by compromising signals either from the outside to the inside (outside-in) of the cell or vice versa (inside-out), thereby regulating cell adhesion, cell spreading and cell motility (22).

Notably, integrins are known to exist in different activity states (23):
- a bent integrin conformation is associated with the low ligand-binding affinity state,
- the extended conformation is associated with the exposed ligand binding site.

While intracellular signaling events can affect integrin activation (inside-out), the activation itself is immediately mediated proximal to integrins, thus enabling potential integrin-focused therapeutic strategies. Recent progress provides insight into the structure of integrin transmembrane domains, and reveals how the final steps of integrin activation are mediated by integrin-binding proteins such as talins and kindlins as summarized by Shattil et al. (24).

The integrin tails have no intrinsic kinase activity, hence they serve as a site for docking of various kinases and related adaptor proteins; here the β tail serves as a primary site in the formation of focal adhesions. By recruitment of most upstream signaling components such as focal adhesion kinases (FAK) as well as src family kinases (SFK), integrins can induce “outside-in” signaling, thereby creating and communicating signals that can induce cell migration or cell proliferation. However, they transmit signals through a variety of intracellular protein kinases and adaptor molecules. For example, integrins have been reported to physically associate with SFK (25), protein tyrosine phosphatases (26), serine and threonine phosphatases (27), C-Src kinase (CSK), IRS-1 (28), and growth factor receptors (29), such as FGF receptor (FGFR) (30).

In this context, CD98hc (4F2hc, SLC3A2) has been characterized recently as the central mediator of adhesion-induced signal transduction via integrins (31–33). CD98hc directly interacts with the cytoplasmic tail of integrin β1A as well as β3, an essential step for initiation of integrins’ outside-in signaling (32, 34–36), thereby influencing integrin dependent cell behaviours (31, 32), including survival, spreading, migration, proliferation and differentiation.

Single amino acid mutations within a conserved motif of the C-terminal end of the cytoplasmic tail of β integrins thereby prevented CD98hc interaction, leading to diminished FAK phosphorylation upon cell adhesion and – as a consequence – reduced cell spreading (32).

A variety of integrins regulate endothelial cell functions such as cell proliferation, survival, migration and invasion during angiogenesis. In endothelial cells, integrins α1β1, α2β1, α4β1, α5β1, α6β1, α6β4, α9β1, αβ3 and αβ5 expression has been described, which allows interaction with extracellular matrix proteins, including fibronectin, fibrinogen, vitronectin, laminin as well as collagens.

Many ligands of integrins – such as αβ3 and αβ5 integrins – are recognized through the Arg-Gly-Asp (RGD) sequence motif, whereas integrin αβ1 recognizes Glu-Ilu-Asp-Val (EILDV). In addition integrin α4β1 / vascular cell adhesion molecule 1 (VCAM-1) interaction has been described to promote tumour angiogenesis (37), because they mediate adhesion of endothelial cells and mural cells during tumour blood vessel formation (37).

Although natalizumab, a blocking antibody against the lymphocyte integrin α4β1, is approved for clinical use for
If any of these procedures are blocked, integrins related functions are hindered, which might lead to potential novel therapeutic strategies. Current studies with anti-integrin therapeutics and preclinical literature give evidence that the most common approach to integrin antagonism includes targeting at or nearby receptor binding sites, although new insights suggest alternative approaches targeting integrin downstream signaling (50).

**Cilengitide**

Numerous antagonists for integrins have been established to be non toxic seeing that they are only expressed on activated or remodeling tissues such as tumours, among them cilengitide (EMD 121974) is a cyclic RGD-peptide inhibitor of \( \alpha v \beta 3 \) and \( \alpha v \beta 5 \) integrins. Significantly enhanced progression free survival was observed in a phase I/IIa clinical trial for glioblastomas (51).

Cilengitide is currently in clinical phase III studies for glioblastomas and in phase II studies for several other tumour identities including breast cancer, squamous cell cancer, non-small cell lung cancer and melanoma (52–55).

Cilengitide is able to
- detach cells that have already adhered to the matrix at concentrations almost equal to concentrations known to prevent cell attachment,
- diminish cell growth, cell proliferation and cell survival in vitro.
- Moreover, it blocks FAK-, Src-, Akt- and Erk signaling pathways (56, 57).

As the interaction of tumour cell with endothelial cells is up to now not fully understood, further experimental approaches have to be done to understand this complex interplay (50).

**Abergrin**

Another \( \alpha v \beta 3 \) antagonist is abergrin (Medi-522) a humanized antibody against \( \alpha v \beta 3 \) integrins and this was also the first anti-integrin therapeutic tested in clinical trials for malignant tumours (58). The antibody
- blocks binding to vitronectin and fibrinogen,
- prevents cell adhesion, migration, proliferation and integrin mediated cell signaling in a dose dependent manner (59).

Tumours of patients with a high expression of \( \alpha v \beta 3 \) have a poorer prognosis than patients with lower \( \alpha v \beta 3 \) expressing tumours. This is consistent with findings that high expression of \( \alpha v \beta 3 \) in tumours is accompanied with an aggressive phenotype and allows metastatic potential and invasive traits. Furthermore, association of \( \alpha v \beta 3 \) with Src promotes attachment autonomous cell growth and \( \alpha v \beta 3 \) integrin mediated FAK signaling fosters the survival of cancer stem cells (60).

**Volociximab**

As mentioned, \( \alpha v \beta 1 \) integrin antagonists are also under development for treatment of malignant tumours. Volociximab is a chimeric human-mouse monoclonal antibody binding to human and rabbit but not to mouse \( \alpha v \beta 1 \) integrins (61). Volociximab is able to
- induce cell death and
- prevent capillary tube formation in vivo when binding to \( \alpha v \beta 1 \) integrins thereby inhibiting signaling cascades.

Because there is no effect on cell proliferation when combined with VEGF blocking antibody it is suggested that volociximab blocking of \( \alpha v \beta 1 \) is downstream the VEGF induced pathway thus independent of growth factor stimulation. In vivo, volociximab shows also anti-tumour as well as anti-angiogenic effects (62).

In a phase II study it showed promising potential efficacy in prolonging disease progression and overall survival.

In patients with clear cell renal cell carcinoma, volociximab delayed disease progression up to 22 months.

Additional phase I and II trials with volociximab used as single agent as well as in combination regiments, are currently on-
going for the treatment of metastatic melanoma, non-small cell lung cancer and peritoneal cancer (61).

**CNTO 95**

Because integrin $\alpha v\beta 3$ and $\alpha v\beta 5$ both regulate angiogenesis a human monoclonal antibody directed against both was developed: CNTO 95. It reduces angiogenesis and tumour growth in human melanoma xenografts in nude mice and rats (63). CNTO 95 was recently tested in clinical phase I/II trials for treatment of melanoma (64).

Integrin targeting therapeutics

During adulthood the majority of blood vessels remain quiescent, and angiogenesis occurs only during embryonic development. However, in many diseases angiogenesis becomes activated, such as during tumour growth and metastasis as well as ocular and inflammatory diseases. Huge advance have been achieved over the last two decades in finding and engineering integrin targeting therapeutics, as integrin expression or functions are changed in many disorders. Progress in the structural characterization of the complex integrin-ligand binding interaction led to the development and design of powerful and selective blocking agents for different integrins, thereby aiming to interfere with angiogenesis, tumour growth and metastasis.

Proteolytic enzymes

Whenever endothelial cells are activated by pro-angiogenic stimuli, they become polarized, loose the cell-to-cell contacts and transmigrate through the basal membrane. During this process, a proteolytic machinery has to be formed at the leading edge of the endothelial cells to degrade matrix proteins. Thereby, proteases are essential of the

- urokinase/plasminogen-system,
- matrix-metalloproteinases system,
- members of the heparanase families,
- chymase.

Thus, it has been shown that interfering with binding of MMP-2 to $\alpha v\beta 3$ integrins by PEX, the non-catalytic fragment of...
MMP-2, inhibits tumour angiogenesis (66). However, high expression of the tissue inhibitor of MMP-1 (TIMP-1) correlates with poor prognosis in cancer (67–69). This fact suggests that TIMP-1 may have activity beyond that of an MMP inhibitor.

Recently, TIMP-1 upregulation has been shown to be involved in mechanisms of developed resistance to anti-VEGF treatment and it is therefore likely to become more important in future research on angiogenesis. Thus, extracellular matrix-degrading enzymes, including MMP-2 and MMP-9, are thought to play key roles in angiogenesis by binding to docking sites on the cell surface after activation by plasmin- and /or membrane-type (MT) 1-MMP-dependent processes. Thereby, MMP-2 binds to MT1-MMP, which itself interacts with αvβ3 integrins.

In contrast, with wild-type explants, tissues isolated from MT1-MMP–/– mice are completely unable to generate neovessels during a seven days in culture, emphasizing the functional role of MT1-MMP during angiogenesis (70).

Urokinase/plasminogen-system

Another proteolytic system, which becomes upregulated by hypoxia or pro-angiogenic growth factors such as FGF-2 or VEGF is the plasminogen-system. In particular the urokinase-type plasminogen activator (uPA), its cell surface receptor uPAR (CD87), a GPI-anchored protein lacking a transmembrane domain, and its inhibitor PAI-1 play an important role in pro-angiogenic endothelial cell behaviour. As well as active uPA, uPAR binds pro-uPA with high affinity in a pocket comprised of all three domains (1 nmol/l) (71). In the linker region between domain 1 and 2 uPAR can be cleaved, giving rise to a membrane-bound truncated molecule (D2D3), which is still active (72).

Thus, it was shown that D2D3 (aa 88–274) directly binds to FPRL1/LXA4R, a G protein-coupled receptor, thereby mediating the chemotactic activity of uPA (73). Furthermore, uPA/PAI-1 binding to uPAR leads internalization of the complex via interaction with members of the LDLR-family (74). Whereas uPA/PAI-1 becomes degraded, uPAR can recycle back to the cell surface (75).

Another important regulator of the uPA system in the mannose 6-phosphate / insulin-like growth factor 2 receptor (M6P/IGF2R), which has been shown to be essential for regulation of endothelial cell invasion in vivo (76, 77).

That uPAR is tightly regulated with cell density was shown recently. Thus, uPAR expression on the surface of confluent endothelial cells is down-regulated compared with subconfluent proliferating endothelial cells. Thereby, uPAR expression is tightly regulated by extracellular signal-regulated kinase 1/2 (ERK1/2) activation, a downstream signaling event of the VEGF / VEGF-receptor system. In confluent cells, however, the receptor-like protein tyrosine phosphatase DEP-1 (density enhanced phosphatase-1/CD148) is abundantly expressed, thereby regulating ERK1/2 activity. As a consequence, uPAR expression is down-regulated. That DEP-1 is not only a regulator of uPAR expression, but thereby regulating angiogenic endothelial cell behaviour, was recently demonstrated by Brunner et al. (78).

Proteolysis regulated by VEGF

When endothelial cells become activated by VEGF, a variety of pro-angiogenic enzymes become transcriptionally upregulated and become secreted as inactive zymogens. Recently, we identified a mechanism of VEGF-induced rapid increase in proteolytic activity on the surface of endothelial cells. In detail, VEGF by binding to its receptor-2 (VEGFR-2, flk-1) induces a phosphatidylinositol 3-kinase (PI3-kinase) dependent change in integrin β1 activity, which leads to activation of pro-MMP-2 as well as pro-uPA (79).

As a consequence, whenever uPAR bound uPA becomes inactivated by PAI-1, the so formed complex becomes internalized by members of the LDLR family, involving clathrin-coated vesicles (80). In turn, uPAR recycles back by a regulated mechanism and becomes focused at the leading edge of migrating endothelial cells. Therefore, uPAR is mainly found in newly formed focal adhesions co-localizing with integrin adhesion receptors.

In contrast to wild type endothelial cells, the VEGF-induced uPAR internalization and recycling was not observed in endothelial cells derived from PAI-1–/– mice, indicating that uPAR internalization in response of VEGF is PAI-1 dependent (80).

Interfering with this chain of event either by blocking uPAR-complex, LDLR interaction using the receptor associated protein (RAP) or by using endothelial cells derived from uPAR–/– deficient mice or by cleaving the GPI-anchor of uPAR, led to a significant downregulation of VEGF-induced endothelial cell migration in vitro and in vivo (80).

Notably, during placental-like growth factor (PIGF) induced endothelial cell migration, pro-uPA activation and consequently uPAR redistribution is not affected. Therefore, we conclude that during VEGF-induced endothelial cell migration focusing of proteolytic enzymes is essential to mediate effective matrix protein degradation. Degradation of extracellular matrix proteins is thought to set free matrix bound PAI-1, which in turn forms a complex with uPAR-bound uPA, leading to internalization of the so formed ternary complex. Although other mechanisms have been described for localized enzyme activation, at least in VEGF-stimulated endothelial cell migration the presence of uPAR seems to be essential. This is consistent with findings obtained by Bajou et al. that tumour angiogenesis is impaired in tumour transplants into PAI-1–/– mice (81).

To guarantee endothelial cell survival during cell migration and invasion, uPAR also increases anti-apoptotic mechanisms. Whenever endothelial cells loose cell-cell contacts and invade into surrounding matrix, they become more prone to apoptosis. Thus, an increase in pro-survival stimuli is essential to avoid apoptosis and guarantee all other steps of angiogenesis. While VEGF via VEGFR-2 has been shown to induce cell survival mainly in a PI3 kinase/Akt-dependent manner (82, 83), uPA also protects against apoptosis by transcriptional up-regulation and partially by mRNA stabilization of inhibitor of apoptosis proteins. Thereby, most prominently the X-linked
inhibitor of apoptosis protein (XIAP) becomes expressed (84). In detail, the anti-apoptotic activity of uPA is dependent on its protease activity, it has to be bound to its receptor uPAR and to interact with the low-density lipoprotein receptor-related protein (LRP).

As a consequence, uPA-induced cell survival induces nuclear factor kappaB (NF-kappaB) p52 activation, as blocking of NF-kappaB activation by using specific NF-kappaB inhibitors abolishes uPA-induced cell survival as it blocks uPA-induced XIAP up-regulation. That this mechanism has a functional role in VEGF-induced cell survival was demonstrated in uPA+/- endothelial cells, which revealed a defective VEGF-dependent up-regulation of XIAP. This is consistent with independent findings that XIAP is an important regulator of VEGF-dependent endothelial cell survival (85).

Thus, uPAR does not only represent a central regulator of endothelial cell surface bound proteolytic activity, but also represents a central regulator of intracellular signal transduction leading to enhanced cell survival via upregulation of anti-apoptotic molecules.

The GPI-anchored protein uPAR has to interact with transmembrane proteins to transmit intracellular signal transduction. Thus, several interaction partners have been identified, which are involved in uPAR initiated signaling. Beside the mentioned G-protein coupled receptor FPRL-1, reciprocal modulation of uPAR dependent biological responses can simultaneously involve EGFR and integrin adhesion receptors, members of the LDLR-family and integrins or matrix metalloproteinases (86). In addition, uPAR interacts with the somatomedin B domain (SMB) of the matrix protein vitronectin, an interaction which involves uPA binding (87). In addition, uPAR has been shown to interact with integrin adhesion receptors via domain 3 (88), among them it seems that uPAR mainly interacts with the fibronectin receptors α5β1, α5β1, but also with αvβ3 and αvβ5 (89). Thus, it is thought that uPAR interacts with integrins via a surface loop within the β-propeller (W 4BC loop) of the alpha chain.

One proposed model how uPAR might affect adhesion-induced signal transduction is that uPAR induces binding of α5β1 to Fn type III repeats 12–15 in an RGD-independent manner, which is in addition to type III repeats 9–11 bound by α5β1 (90). On the other hand, it was shown recently that uPAR negatively regulates integrin function via mediating their endocytotic clearance by LRP, leading to cell detachment (91), which is consistent with findings that uPAR regulates integrin redistribution (92).

Thus, a tight collaboration between adhesion molecules and proteolytic systems is essential to guarantee most effective cell motility.

### Biomarkers

Since VEGF represents the main pro-angiogenic stimulator (1), it is currently in focus for therapeutic interventions and has resulted in the registration of bevacizumab by the FDA and EMEA for the treatment of mCRC (93) and other malignancies. Nevertheless, the use of VEGF-targeting drugs has been shown to be of limited efficacy (12, 13) and for those that do, responses are short-lived, and resistance develops in the majority of patients. For instance, the benefit in overall survival upon addition of the anti-VEGF monoclonal antibody (mAb) bevacizumab to chemotherapy with advanced stage non-small cell lung cancer or colorectal cancer is relatively short, averaging less than two months in the most recent trials (13, 94). Notably, there are a number of negative phase III trials with VEGF-targeted therapy.

Thus, it is essential to identify biomarkers to predict a therapeutic benefit for bevacizumab and identify those patients who are more prone to benefit from this therapeutic option.

However, so far risk stratification methods for VEGF-directed treatment of malignant disease remained futile: Determining VEGF expression levels has been shown in a retrospective analysis of 278 patients suffering from advanced colorectal cancer to be not predictive to a bevacizumab based therapy (95). This negative data on VEGF as a predictive marker was also confirmed by a study determining VEGF plasma level modulations during treatment with bevacizumab, which revealed no such association during bevacizumab treatment on mCRC patients (96).

However, in the ECOG 2100 phase III breast cancer trial comparing paclitaxel versus paclitaxel plus bevacizumab, determination of VEGF-1154 AA and VEGF-2578 AA genotypes in the combination treatment arm revealed a superior median overall survival compared with patients with alternative genotypes and were therefore predictive (97). This effect might be explained by the observation that the –2578CC and –1154GG genotypes have altered VEGF secretion.

Another prospective approach aimed to identify biomarkers related to hypoxia, angiogenesis or EGFR in recurrent glioblastoma multiforme. None of the biomarker immunohistochemical tested alone or in combination could identify a patient population likely to benefit from bevacizumab and irinotecan (98).

Although not predictive, a recent study suggested that changes in plasma cytokines and angiogenic factors (CAFs) during bevacizumab-based treatment with a rise in alternate pro-angiogenic cytokines and myeloid recruitment factors before radiographic progression might represent mechanisms of resistance (96). Several pro-angiogenic cytokines were elevated before progression, notably FGF-2, PIGF, and HGF. At the time of radiographic progression, FGF-2, and MMP-9 were increased. It is intriguing to speculate that those hypoxia-induced angiogenic growth factors might bypass the anti-angiogenic effect of bevacizumab.

### Perspectives

Targeting VEGF has been shown to be effective only in combination with chemotherapy.

Therefore, anti-VEGF therapy is currently considered as a chemotherapy sensitizer to the tumour vasculature promoting the delivery of nonspecific agents to the tumour tissue.
A novel anti-VEGF approach is the VEGF trap afibrecet, consisting of the VEGFR extracellular domain fused to the IgG1 Fc portion. Afibrecet has been combined with a number of cytotoxic agents (platin, irinotecan, docetaxel) in ongoing clinical phase I, II, and III studies. However, a major challenge in using anti-VEGF agents is identifying validating predictive and prognostic molecular or cellular markers, which identify the subgroup of patients most likely to benefit from this therapeutic approach.

Novel therapeutic approaches aim to replace the rather unspecific multiple-targeting kinase inhibitors, such as sunitinib, which affects many kinases (VEGFR-1 to -3, PDGFR, Flt-3, c-KIT) and thereby might cause significant haematologic toxicity. A novel more specific approach is axitinib, which revealed in the phase 3 AXIS 1032 trial a significant benefit PFS in previously treated renal cell cancer (RCC) when compared to sorafenib (99). Besides receptor tyrosine kinases, other therapeutic approaches aim to use as a target other major angiogenic molecules, among them – as mentioned – adhesion receptors or proteolytic enzymes.

However, we need as a prerequisite an improved biological understanding of the physiology of the angiogenic process to determine individual targets and develop more efficacious anti-angiogenic therapies.

Thereby, an individualized combination of specific anti-angiogenic drugs might lead to less toxic but more efficient therapeutic option in the treatment of cancer.

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Conflict of interest
The authors declare, that they have no conflict of interest.

References
12. Cassidy J, Clarke S, Diaz-Rubio E et al. Randomized phase III study of capcitabine plus oxaplatin in lung cancer, which revealed in the phase 3 AXIS 1032 trial a significant benefit PFS in previously treated renal cell cancer (RCC) when compared to sorafenib (99). Besides receptor tyrosine kinases, other therapeutic approaches aim to use as a target other major angiogenic molecules, among them – as mentioned – adhesion receptors or proteolytic enzymes.

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92. Navotny r, Unseld M, Poettler M et al. Urokinase receptor (uPAR)-dependent integrin redistribution represents a central mechanism for growth factor induced endothelial cell migration. ASH Annual Meeting 2010: Abstr. 2119.