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Integrin signaling modes controlling cell migration and metastasis

Truong, H.H.

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Chapter 5

Integrins: Signaling Disease, and Therapy

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Integrins: Signaling, disease, and therapy

STEPHAN HUveneERS, HOA TRUONG, & ERIK H. J. DANEN

Division of Toxicology, Leiden/Amsterdam Center for Drug Research, Leiden University, Leiden, The Netherlands

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Abstract

Background: Integrins are a family of transmembrane receptors that mediate cell-cell and cell-matrix adhesion. They are involved in stable cell adhesion and migration of cells. In addition, integrin-mediated interactions modulate the response to most, if not all growth factors, cytokines, and other soluble factors.

Purpose: In this review, we briefly explain how integrins can affect the multitude of signal transduction cascades in control of survival, proliferation, and differentiation. Subsequently, we primarily focus on targeting integrins $\alpha 5 \beta 1$ and $\alpha v \beta 3$ in disease and we discuss how antagonists of these integrins, including disintegrins, RGD peptides, small molecules, and function blocking antibodies, may be of therapeutical value either alone or, especially in the treatment of cancer, in combination with existing therapeutical strategies.

Keywords: *Adhesion, treatment, cancer*

Introduction

Integrins are cell surface receptors that mediate interactions with the extracellular matrix (ECM) or with counter-receptors on other cells. They cluster and recruit a large multi-protein complex to cell-ECM or cell-cell junctions, which connects them to the cytoskeleton. In addition, signaling proteins and their substrates accumulate at these sites, which regulate the stability of the adhesions and control cytoskeletal dynamics. Besides their critical role in stable cell adhesion and cell migration, integrin-mediated interactions modulate signaling by various other receptors including receptor tyrosine kinases (RTK), G-protein-coupled receptors, cytokine receptors, and others. Consequently, integrins play important roles in survival, proliferation, and differentiation. They are also implicated in several human diseases and integrin antagonists have been tested in preclinical models for various diseases including inflammation, thrombosis, arthritis, and cancer and some have even entered clinical trials. For the treatment of cancer, the expectation is that these antagonists may increase the efficacy of radio- and chemotherapy.

Integrins

Integrins are heterodimeric transmembrane receptors that bind with their globular head domain to components of the ECM. Some integrins can also bind counter receptors present on other cells, bacterial polysaccharides, or viral coat proteins. Intracellularly, integrins are connected via associated proteins to the actin cytoskeleton. 18α and 8β subunits are encoded in the human genome from which 24 different functional integrins are currently known to be generated (van der Flier & Sonnenberg 2001, Hynes 2002). Ligand binding can be regulated through integrin clustering and through modulation of the activity of individual integrins which involves the propagation of conformational changes from the cytoplasmic tails across the membrane towards the ligand-binding region (Liddington & Ginsberg, 2002). Integrins can also activate intracellular signal transduction cascades, a process referred to as 'outside-in signaling'. Integrin-mediated cell adhesion can trigger calcium fluxes, activate tyrosine and serine/threonine protein kinases and inositol lipid metabolism, and regulate the activity of the Rho family of small GTPases (Danen & Yamada 2001).

Correspondence: Erik H. J. Danen, Division of Toxicology, Leiden/Amsterdam Center for Drug Research, Leiden University, Leiden, The Netherlands.
E-mail: e.danen@lacdr.leidenuniv.nl

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Genetic studies in flies, worms, and mice have established important roles for integrins and integrin-associated proteins in the development and maintenance of tissues and in the progression of diseases (De Arcangelis & Georges-Labouesse 2000, Bouvard et al. 2001, Bokel & Brown 2002).

Integrin signaling

Integrins generally contain a short cytoplasmic domain which is devoid of enzymatic activity. Therefore outside-in signaling by integrins largely depends on interactions with neighbouring receptors, adaptor and signaling proteins.

Nevertheless integrin signaling is critically important for regulation of signal transduction pathways through distinct mechanisms (Figure 1):

- (1) Integrins and growth factor receptors may activate parallel pathways that synergize at the level of activation of downstream signaling proteins. In this way threshold levels in signaling pathways can be lowered considerably (Chen et al. 1996, Renshaw et al. 1997).

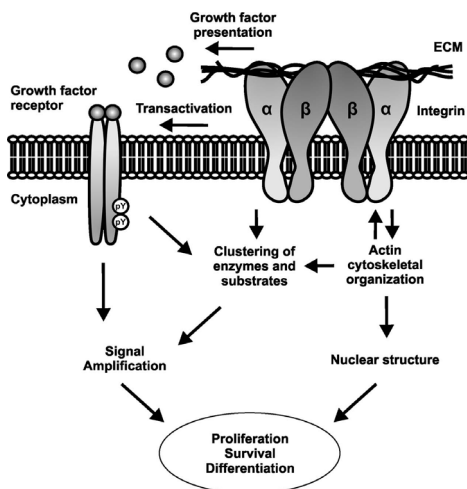


Figure 1. Cross-talk between growth factor receptors and integrins. Integrins affect signal transduction pathways through distinct mechanisms: (1) Together with growth factor receptors, integrins activate parallel pathways that synergize at the level of downstream signaling proteins; (2) Integrins initiate clustering of proteins in cell-matrix adhesions, thereby bringing kinases and substrates in close proximity; (3) Those cell-matrix adhesions also anchor the actin cytoskeleton and thereby generate cytoskeletal tension that affects the nuclear shape and gene expression; (4) Integrin-mediated adhesion can cluster and transactivate receptor tyrosine kinases, and (5) integrins organize the extracellular matrix and thereby regulate upstream signaling of receptors. See text for additional details.

- (2) Cell-matrix adhesion initiates clustering of integrins in the plane of the membrane and reorganization of the actin cytoskeleton, which further stimulates the organization of integrins and associated proteins into large multi-protein platforms like focal adhesions, hemidesmosomes or podosomes. In those platforms integrins may increase signals generated by growth factor receptors by bringing kinases and substrates in close proximity (Burridge & Chrzanowska-Wodnicka 1996, Geiger et al. 2001).
- (3) Cell-matrix adhesions act as anchoring sites for the actin cytoskeleton and as such they allow the generation of tension and shape changes. Via cytoskeletal connections with the nucleus such changes can affect the nuclear shape and chromatin structure which might explain the profound effect of integrin-mediated cell adhesion on the expression of genes (Maniotis et al. 1997, Lelievre et al. 1998).
- (4) Integrin-mediated adhesion can cluster and transactivate several RTK including platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), Ron, Met, and vascular endothelial growth factor receptor (VEGFR) (Yamada & Even-Ram 2002) and members of the Src family kinases (Shattil 2005).
- (5) Integrins regulate RTK signaling further upstream through their ability to organize the ECM. Proteoglycans in the ECM can bind and structurally modify various growth factors and integrin-mediated cell adhesion then allows their subsequent presentation to growth factor receptors (Faham et al. 1998). Through these mechanisms integrins play an essential role in regulating signaling pathways in control of survival, proliferation, and differentiation both in health and disease.

Survival

Most adherent cell types depend on integrin-mediated adhesion for survival (Giancotti & Ruoslahti 1999, Cordes 2006, Gilcrease 2007). Loss of adhesion causes cells to undergo apoptosis, a process referred to as anoikis (Frisch & Screaton 2001). Likely, anoikis is important to maintain the integrity of tissues by preventing cells from growing at inappropriate sites after losing adhesion from their original surrounding. Integrin-mediated cell adhesion in 2-dimensional culture systems stimulates phosphatidylinositol-3-kinase (PI3K)-mediated protein kinase B (PKB/AKT) activity and B-cell leukemia-2 (Bcl-2) expression which mediates survival signals (Giancotti & Ruoslahti 1999). In absence of serum factors

integrin-mediated adhesion to fibronectin enhances survival by activating c-Jun N-terminal kinase (JNK) in a focal adhesion kinase (FAK) dependent manner (Almeida et al. 2000). Integrin $\alpha 6 \beta 4$ ligation also supports nuclear factor κB (NF κB)-mediated survival signals in 3-dimensional cultures of mammary epithelial cells (Weaver et al. 2002). On the other hand, integrins that are not ligand-bound can trigger apoptosis of fully adherent cells by recruitment and activation of caspase-8 suggesting that a given integrin expression profile renders a cell dependent on a specific ECM environment for its survival (Varner et al. 1995, Stupack et al. 2001).

Proliferation

The ability to grow in the absence of cell adhesion is a key property of oncogenically transformed cells. In normal untransformed cells, integrin-mediated cell adhesion regulates the G1 phase of the cell cycle (Assoian & Schwartz 2001). Integrins cooperate with RTK to stimulate the cyclin E/cyclin dependent kinase 2 (cdk2) activity that drives S-phase entry. Multiple different pathways have been described to connect integrins to cell cycle progression. Regulation of cyclin D1 expression, both at the level of gene transcription and protein accumulation, is a key element of the control of cell cycle progression by RTK and integrins. Control of extracellular signal-regulated kinase (ERK) activation can largely explain the transcriptional regulation of cyclin D1 by integrin-mediated adhesion.

Mitogen-stimulation of RTK and integrin-mediated adhesion can each independently stimulate ERK activation. However, only when adherent cells are stimulated with mitogens ERK activity is strong and sustained due to convergence of RTK and integrin signaling at the level of Raf or MAP/ERK kinase (MEK) (Chen et al. 1996, Renshaw et al. 1997).

There are several ways through which integrins can regulate ERK activity (Howe et al. 2002):

- (1) Binding of integrins to the ECM stimulates the formation of an active FAK/Src signaling complex at sites of adhesion. Autophosphorylation of FAK at Tyr³⁹⁷ following integrin-mediated adhesion creates a binding site for the Src homology 2 (SH2) domain of Src (Schlaepfer & Hunter 1998). Subsequently, Src can phosphorylate other Tyr residues of FAK thereby creating binding sites for downstream effectors. Direct binding of growth factor receptor binding protein-2 (Grb2) to the active FAK/Src complex or indirect binding through Shc stimulates the Grb2-Sos-Raf-MEK-ERK pathway. Alternatively, Src can phosphorylate the scaffolding protein p130Cas (Crk associated substrate) that

is also associated with FAK via its SH3 domain, thereby creating a binding site for the adaptor protein Crk. Either through association with son of sevenless (Sos) or through association with C3G (a guanine-nucleotide exchange factor for the small GTPase Rap-1), the interaction with Crk can result in ERK activation. Integrin-mediated adhesion also stimulates the association of the adaptor protein Nck with p130Cas, creating yet another potential link from p130Cas to ERK activation. Finally, PI(3)K can associate with phosphorylated Tyr³⁹⁷ in FAK and it may become activated upon integrin-mediated cell adhesion. PI(3)K may activate ERK through its role as a protein kinase or through modulation of Sos activity via its production of phosphatidylinositol-3,4,5-trisphosphate (PtdInsP3).

- (2) Secondly, certain integrin α -subunits are coupled to the Src family kinase Fyn through association with the oligomeric transmembrane protein Caveolin-1 (Guo & Giancotti 2004). Upon integrin ligand binding, Fyn is activated and it subsequently recruits and phosphorylates Shc, creating a link to the Grb2-Sos-Ras-Raf-MEK-ERK pathway.
- (3) Finally, integrin-mediated adhesion activates protein kinase C (PKC) and several PKC isoforms can directly activate Raf. Enhanced levels of phospholipids probably can explain the activation of PKC upon integrin-mediated adhesion. Also integrin-mediated adhesion leads to the activation of the p21-activated protein kinases (PAK) through several mechanisms, and PAK can activate both Raf and MEK.

Besides controlling ERK activity, suppression or relocalization of the cyclin dependent kinase inhibitors p21 and p27 by integrin-mediated adhesion also contributes to G1 cell cycle progression. Additionally, integrin-mediated adhesion increases expression of c-Myc through activation of c-Src (Benaud & Dickson 2001). The organization of the actin cytoskeleton by integrins is essential for adhesion-regulated proliferation and integrin-mediated control of the activity of Rho GTPases (enzymes critically involved in actin cytoskeletal organization) is an important aspect of adhesion-mediated regulation of the levels of cyclin D1 and cdk-inhibitors.

Differentiation

Integrin-mediated cell adhesion also regulates the expression of genes related to differentiation. Adhesion to basement membrane components stimulates the synthesis of milk proteins by increasing

phosphorylation of the prolactin receptor in cultured mammary epithelial cells (Li et al. 1987, Edwards et al. 1998). Integrin-mediated adhesion also primes monocytes for inflammatory responses (Haskill et al. 1988, Shi & Simon 2006). Another example of regulation of differentiation by integrins is the inhibition by integrin-blocking antibodies of the formation of contracting myotubes and expression of meromyosin by embryonic myoblasts (Menko & Boettiger 1987). Deletion of $\beta 1$ integrins in embryonic stem (ES) cells showed that $\beta 1$ is important for normal *in vitro* cardiac and myogenic differentiation, whereas neuronal differentiation is accelerated in $\beta 1$ -deficient ES cells (Fassler et al. 1996, Rohwedel et al. 1998). Finally, terminal differentiation of cultured keratinocytes under semi-solid conditions is inhibited by the integrin-ligand fibronectin or by adhesion-blocking antibodies to $\beta 1$ integrins (Watt 2002). Moreover, a tumor-associated mutation in $\beta 1$ was recently found that increases ligand binding and prevents terminal differentiation of keratinocytes which might contribute to the formation of epidermal neoplasia (Evans et al. 2003).

Integrins in disease

Aberrant cell adhesion and migration have been implicated in several diseases, including a number of inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease and asthma, as well as cardiovascular diseases, thrombosis, and cancer. This often correlates with alterations in the expression or functionality of integrins. For instance, deletion of the $\alpha 6 \beta 4$ integrin leads to a skin blistering disease termed Epidermolysis bullosa (Borradori & Sonnenberg 1999), deletion of $\alpha 7 \beta 1$ causes congenital muscular dystrophy (Vachon et al. 1997), and in patients with Glanzmann's Thrombasthenia platelets fail to aggregate, due to quantitative or qualitative defects of $\alpha IIb \beta 3$ (Hodivala-Dilke et al. 1999). On the other hand, in osteoporosis up-regulation of integrin $\alpha v \beta 3$ causes enhanced bone resorption by osteoclasts (Lakkakorpi et al. 1993) and high expression levels of various types of integrins have been correlated with tumor progression in a numbers of cancers (Mizejewski 1999).

The use of integrin antagonists

Integrin-blocking strategies have been developed to treat a large number of diseases (Table I). Integrin antagonists comprise small molecule compounds, peptidomimetics, and monoclonal antibodies (mAb). We will discuss use and action of several drugs with focus on cancer and antagonists of the integrins $\alpha 5 \beta 1$ and $\alpha v \beta 3$, being the most extensively studied targets in this disease.

Anti-angiogenesis is an emerging approach for cancer treatment. Angiogenesis, which is the formation of new blood vessels, is a vital process for tumor progression (Folkman 1971). Inhibition of new blood vessel formation has been shown to block the growth and spread of solid tumors in various animal models. There is substantial evidence that several integrins, including $\alpha v \beta 3$, $\alpha v \beta 5$, and $\alpha 5 \beta 1$ have an important role in tumor angiogenesis (Brooks et al. 1994a, Friedlander et al. 1995, Kim et al. 2000). The regulation of cell migration and survival of endothelial cells during angiogenesis and metastasis via these integrins makes them suitable targets for anti-angiogenic therapy.

Disintegrins and RGD peptides

The RGD sequence is an important cell attachment recognition site for integrins in many ECM components (Pierschbacher & Ruoslahti 1984, Gardner & Hynes 1985, Ploew et al. 1985) and has been used as a pharmaceutical application to treat aberrant cell adhesion related-diseases. Disintegrins are RGD-containing cysteine-rich peptides discovered in snake venoms (Gould et al. 1990). Some disintegrins specifically bind to integrin $\alpha v \beta 3$ and are applied as therapeutic agents for angiogenesis-dependent tumor growth and metastasis (Huang 1998). Others, such as Contortrostatin, which is a disulfide-linked homodimer of 13.5 kDa containing two RGD sites isolated from the venom of *Agekistrodon contortrix*, can bind $\alpha v \beta 3$, $\alpha v \beta 5$, as well as $\alpha 5 \beta 1$ and have been shown to inhibit tumor growth and angiogenesis in an orthotopic xenograft model for breast cancer (Swenson et al. 2005).

The disadvantage of natural occurring peptides such as disintegrins is their relatively large size and low metabolic stability, which limits their usefulness for clinical application (McLane et al. 2004, Cai & Chen 2006). RGD peptides have been further optimized by incorporation of D-amino acids and use of cyclic structures. Cyclic RGD-containing pentapeptides are the most commonly used RGD-based $\alpha v \beta 3$ antagonists (Ruoslahti 1996). Cyclo (RGDFV) is a highly effective $\alpha v \beta 3$ antagonist with anti-tumor and anti-angiogenic effects (Brooks et al. 1994b, Friedlander et al. 1995). In a xenograft model for melanoma cyclo (RGDFV)-treatment hindered tumor growth and histological analysis indicated that the effect results from angiogenesis inhibition rather than inhibition of tumor cell $\alpha v \beta 3$ (Dechantsreiter et al. 1999). Systematic modification of this peptide resulted in a more active and selective compound named c(RGDf(NMe)V) also known as Cilengitide (EMD 121974) (Goodman et al. 2002). Cilengitide induces apoptosis in Glioblastoma and

Table I. Integrin antagonists and its targeted diseases.

Integrin target	Drug	Company	Disease	Reference
$\beta 2$	Efalizumab (RabTIVA [®])	Genetech	Psoriasis	(Lebwohl et al. 2003)
$\alpha 4$	Natalizumab (Tysabri [®])	Biogen Idec & Elan	MS, Crohn's disease	(Miller et al. 2003, Ghosh et al. 2003)
$\alpha 4\beta 1/\alpha 4\beta 7$	TR14035	N/A	Asthma	(Cortijo et al. 2006, Sircar et al. 2002)
$\alpha 4\beta 7$	MLN02	Millennium pharmaceuticals	Ulcerative colitis	(Feagan et al. 2005)
$\alpha 5\beta 1$	Volociximab (M200/Gemzar [®])	PDL Biopharma Inc	Renal cell carcinoma, metastatic melanoma, pancreatic cancer	www.clinicaltrials.gov
	Endostatin TM ATN-161	EntreMed Inc. N/A		(O'Reilly et al. 1997) (Stoeltzing et al. 2003, Livant et al. 2000)
$\alpha v\beta 3$	Chimeric 7E3 Fab (Abciximab/ReoPro [®])	Centocor		(Trikha et al. 2002)
	Contortrostatin	N/A		(Clark et al. 1994, Trikha et al. 1994)
	C(RGDf(NMe)V) (Cilengitide, EMD 121974)	Merck KGaA	Angiogenesis, cancer	www.cancer.gov/clinicaltrials (Albert et al. 2006, Taga et al. 2002)
	C (RGDfV) cyclo (Arg-Gly-Asp-D-Phe-Val)	N/A		(Allman et al. 2000, Friedlander et al. 1995, Brooks et al. 1994b, Dechantsreiter et al. 1999)
	S247	Pharmacia Corp		(Reinmuth et al. 2003, Abdollahi et al. 2005)
	Resveratrol	N/A		(Aggarwal et al. 2004)
	Vitaxin SB273005	MedImmune Inc. SmithKline Beecham Pharmaceuticals	Rheumatoid arthritis	(Mikecz 2000) (Badger et al. 2001)
	SC55631	N/A	Osteoporosis	(Engleman et al. 1997)
$\alpha IIb\beta 3$	Chimeric 7E3 Fab (Abciximab/ReoPro [®])	Centocor	Unstable angina, restenosis, stroke,	(Bennett 2001)
	Lotrafiban	SmithKline Beecham Pharmaceuticals	acute coronary artery disease	(Liu et al. 2000)

medullablastoma cells (Taga et al. 2002). It is applied in phase I and II to treat non-small lung cancer, prostate cancer, glioblastoma, pancreatic cancer, melanoma, and lymphoma (www.cancer.gov/clinicaltrials).

Small molecule integrin antagonists

There is evidence that small molecule antagonists could be used to treat human diseases, which depend on angiogenesis, including rheumatoid arthritis, osteoporosis, and cancer (Hartman & Duggan 2000, Kerr et al. 2000, Giavazzi & Nicoletti 2002, Shimaoka & Springer 2003). For this purpose, new classes of small molecule $\alpha v\beta 3$ antagonists have been developed, including isoxazolines (Pitts et al. 2000), disubstituted indazoles (Batt et al. 2000), and non-peptide chemical RGD peptidomimetics. An example of this latter class of antagonists, S247, which blocks $\alpha v\beta 3/\alpha v\beta 5$, was shown to decrease tumor

growth and angiogenesis of colon cancer liver metastases leading to prolonged survival in an orthotopic murine model (Reinmuth et al. 2003). Another non-peptide chemical RGD mimetic that targets $\alpha v\beta 3$, SC56631 inhibits bone resorption in vitro and suppresses osteoporosis in oestrogen-deprived animals (Engleman et al. 1997). The naturally occurring polyphenol, Stilbene Resveratrol also binds to integrin $\alpha v\beta 3$ at or near the RGD-binding site and induces apoptosis in cancer cells through activation of ERK with consequent phosphorylation of p53 (Lin et al. 2006). Compared to $\alpha v\beta 3$, few small molecule antagonists are known to inhibit $\alpha 5\beta 1$. Nevertheless, treatment with ATN-161, a non-RGD peptide specific for $\alpha 5\beta 1$ that is derived from the synergy site in fibronectin that is part of the $\alpha 5\beta 1$ -binding motif but not of that of $\alpha v\beta 3$, enhanced the efficacy of chemotherapy in a mouse model for colon cancer metastasis (Stoeltzing et al. 2003).

Monoclonal antibodies

LM609 is an anti-human integrin $\alpha v\beta 3$ mAb that blocks cell adhesion to RGD-containing ligands (Cheresh 1987). It prevents bFGF (basic fibroblast growth factor)- and TNF α (tumor necrosis factor- α)-dependent angiogenesis but has no effect on pre-existing vessels (Brooks et al. 1994a). LM609 was effective in preclinical models for glioblastoma, melanoma, breast, and prostate cancer. Intravenous administration of LM609 inhibited outgrowth of $\alpha v\beta 3$ -negative human breast cancer cells in a combined (SCID) mouse/human chimeric model (Brooks et al. 1995). Fewer human blood vessels and less invasive tumors were observed in these LM609-treated animals with no apparent effect on normal human tissue, indicating that LM609 acts as an anti-angiogenic compound. Similar effects have been obtained with antibodies directed against $\alpha 5\beta 1$ (Kim et al. 2000).

The serum half-life and integrin-binding affinity of LM609 have been improved by generating a humanized version, Vitaxin (Carter 2001, Wu & Senter 2005). Optimization of the complementarity-determining regions further improved Vitaxin's integrin binding affinity allowing it to inhibit tumor growth in Kaposi's sarcoma and partially inhibit the binding of the human immunodeficiency virus-1 (HIV-1) Tat protein to $\alpha v\beta 3$ (Rader et al. 2002). Vitaxin II, although binding $\alpha v\beta 3$ with even higher affinity, showed no positive response in cancer treatment but may be effective as adjuvant in combination with chemo- or radiation therapy (Posey et al. 2001). In 2003, MedImmune licensed Vitaxin II (MEDI-522) for clinical development in phase II trials in prostate cancer, melanoma, psoriasis, and rheumatoid arthritis. However in 2004, the clinical trial of Vitaxin in the treatment of rheumatoid arthritis and psoriasis was ended because preliminary results failed to demonstrate clinical benefits. Nevertheless, the trials for melanoma and prostate cancer are still in progress (MedImmune ends some Vitaxin testing, advanced tests for arthritis treatment halted; cancer research continues. Article by Michael S. Rosenwald, *Washington Post* staff writer; August 31, 2004; Page E05).

Strongly improved versions of antibodies against $\alpha 5\beta 1$ have also been generated. For instance, Volociximab, a chimeric humanized mAb, is a high affinity function inhibitor of the $\alpha 5\beta 1$ integrin, which, like $\alpha v\beta 3$ has been found to be upregulated in activated endothelial cells. It has been applied in clinical phase II trials for solid tumors in renal cell carcinoma, metastatic melanoma and pancreatic cancer. These are ongoing studies with no data reported yet (www.clinicaltrials.gov).

Potential of integrin antagonists to improve efficacy of existing anticancer therapy

Similar to other anti-angiogenic agents, integrin antagonists can be applied in combination with cytotoxic anticancer therapy, such as chemo- or radiotherapy. Such combinational approaches can maximize efficacy in cancer by destroying cancer cells as well as endothelial cells, the latter depriving the tumor of nutrients and oxygen (Teicher 1996). On the other hand, the anti-angiogenic agent may also 'normalize' the abnormal structure and function of tumor vessels, thereby improving drug (but also oxygen) delivery (Jain 2005). Examples of such combination therapies are discussed in the following (Figure 2).

The ATN-161 $\alpha 5\beta 1$ antagonist enhanced the efficacy of chemotherapy in a mouse model for colon cancer metastasis (Stoeltzing et al. 2003). Co-application with Cilengitide increased the anti-tumor effectiveness of a tumor-specific antibody against interleukin 2 (IL-2) fusion proteins in a murine tumor model (melanoma, colon carcinoma, and neuroblastoma) (Lode et al. 1999). In pancreatic cancer, Cilengitide combined with gemcitabine (a radiation-sensitizing agent and a wide spectrum anti-cancer drug) inhibited highly vascularized tumor growth (Colomer 2004, Raguse et al. 2004). In ongoing trials for breast cancer, colon cancer, prostate cancer, melanoma, lung cancer, glioblastoma, and ovarian cancer, Vitaxin II is applied in combination with chemo-, hormonal-, biological-, immuno-, or radiotherapy. Patients with Stage IV

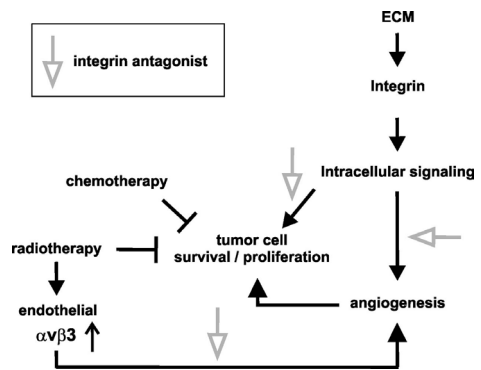


Figure 2. Integrins as targets in anti-cancer therapy. Open arrows indicate processes that are blocked by integrin antagonists. These include survival and proliferation of tumor cells as well as survival, proliferation, and/or migration of endothelial cells. The latter may be of particular importance during radiotherapy where increased expression of $\alpha v\beta 3$ on endothelial cells can mediate therapy escape through enhanced angiogenesis.

melanoma have 9.4-month median survival when treated with Vitaxin II combined with dacarbazine (DTIC) whereas patients treated with DTIC alone, have a median survival of 7.9 months (Cai & Chen 2006). It has been reported that radiotherapy in fact promotes integrin-mediated survival signaling through PKB/Akt by upregulating $\alpha v \beta 3$ expression on endothelial cells. This escape mechanism can be circumvented by administering angiogenesis inhibitors, such as the small molecule $\alpha v \beta 3$ integrin antagonist S247, which prevents radiation-induced PKB/Akt phosphorylation leading to enhanced anti-angiogenic and anti-tumor effects (Abdollahi et al. 2005).

Most integrin antagonists interfere with binding of natural ECM components to their receptors and thereby prevent integrin signaling to survival and proliferation. As such, integrin antagonists may effectively suppress tumorigenesis by targeting these signaling pathways in both tumor and endothelial cells. Ultimately, a trimodal strategy in which radio-, chemo-, and anti-angiogenic therapies are combined may be highly effective in the treatment of cancer. The use of integrin antagonists as anti-angiogenic agents that may also target tumor cells, may fit well in such strategies.

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