Published in final edited form as:
Lymphat Res Biol. 2008 ; 6(3-4): 155–163. doi:10.1089/lrb.2008.1011.

Roles of Integrins in Tumor Angiogenesis and Lymphangiogenesis

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Abstract

The lifelong dedication of Dr. Judah Folkman to understand how tumors co-opt vasculature to promote tumor growth and spread resulted in the development of an astounding body of knowledge and development of new clinical therapeutics for cancer. Angiogenesis is a critical point in the development and dissemination of most human tumors. Tumor-associated lymphangiogenesis also plays an important role in mediating tumor spread to lymph nodes. The molecular regulations of these processes are complex, and many key molecular families have been implicated in the regulation of angiogenesis and lymphangiogenesis. By regulating cell—cell and cell—matrix contacts, integrins participate in blood and lymphatic vessel growth by promoting endothelial cell migration and survival. Understanding the underlying mechanisms by which integrins promote tumor-associated blood and lymphatic vessel development might provide important modalities for the therapeutic intervention of metastatic spread. This review focuses on the role of integrins in angiogenesis and lymphangiogenesis. Integrins represent potential targets for pharmacological agents and open new avenues for the control of metastatic spread in the treatment of malignancies. This article is dedicated to the memory of Dr. Judah Folkman, an amazing and caring teacher, scientist, physician, and friend.

Introduction

Angiogenesis and lymphangiogenesis—the development of new blood vessels and lymphatics from the pre-existing vasculature, respectively—are processes with integral roles in embryonic development and numerous diseases, including cancer progression and metastasis and inflammation (Fig. 1).

Angiogenesis is the better understood of the two processes, in part due to the intense research focus placed upon the field because of the significance of blood vascular development for tumor growth and ischemic disease.[1] Angiogenesis, the process of new blood vessel formation from pre-existing ones, plays a key role in various physiological and pathological conditions, including embryonic development, wound repair, inflammation, and tumor growth. The nascent vascular bed expands by sprouting and matures into a system of stable vessels. Hypoxia is an important stimulus for expansion of the vascular bed.[2] Initially, cells are oxygenated by simple diffusion of oxygen, but when tissues grow beyond the limit of oxygen diffusion, hypoxia triggers vessel growth by signaling through hypoxia-inducible transcription factors (HIFs). HIFs upregulate many angiogenic genes, include the gene for Vascular Endothelial

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Disclosures The authors declare no competing financial interests exist.

Growth Factor (VEGF-A).[3] VEGF-A can bind the receptors VEGFR-1 and VEGFR-2 to induce endothelial cell migration, proliferation, and survival. VEGF-A stimulates physiological and pathological angiogenesis and is therefore currently being evaluated for pro- and anti-angiogenic therapy. To induce angiogenesis, many angiogenic growth factors, including basic fibroblast growth factor (FGF-2)[4] interact with signaling receptors expressed on the endothelial cell (EC) surface that, with some exceptions such as TNF and chemokine receptors,[5] are endowed with tyrosine kinase (TK) activity.[6] Additionally, many angiogenic growth factors are also engaged in multiple interactions in the extracellular environment and on the EC surface.[7] For instance, angiogenic growth factors bind a variety of free or immobilized proteins, polysaccharides, and complex lipids present in the extracellular environment that may affect their integrity, stability, bioavailability, and diffusion.[7] Angiogenesis not only depends on the expression of specific growth factors such as vascular endothelial growth factor and fibroblast growth factor, but also on cell adhesion to the extracellular matrix (ECM). During growth of new blood vessels, adhesion to the ECM via integrins regulates proliferation, survival, and motility of endothelial cells.

The lymphatic vasculature performs a crucial function by transporting fluid and macromolecules, including fat, from tissues back to the blood circulation. It also links tissue fluids to lymph nodes as an immune surveillance system.[8] A lack of molecular markers specific to the lymphatic system has been an impediment to lymphangiogenesis research until recently, when the identification of several such markers, Lyve-1, Prox-1, and Podoplanin, has led to molecular insights into lymphangiogenesis.[9,10] Numerous pathologies are associated with the lymphatics, such as the metastatic spread of cancer, lymphangiomas, lymphangiectasias, and lymphedema. Therapeutic strategies based upon the expanding body of lymphatic knowledge are now being considered.

Metastatic tumor cells can exploit the lymphatic vasculature, as they frequently spread through the lymphatic vessels and colonize lymph nodes. In particular, breast cancer and melanoma are known to spread to lymph nodes, necessitating radical surgery that destroys the lymphatic vessel network and leads to impairment of afferent lymphatic flow. Many patients who undergo radical axillary lymph node dissection subsequently develop lymphedema.[11,12] Clinically, lymphedema presents as visible or palpable tissue swelling. Breast cancer (BC)-related lymphedema is a chronic condition that diminishes quality of life and contributes to impairments in limb range of motion, loss of strength, and functional limitations with activities, such as lifting and reaching.[13,14]

Growth factors capable of directly inducing the growth of lymphatic vessels have been characterized. These factors, VEGF-C and VEGF-D, are ligands for the endothelial cell-specific tyrosine kinase receptors VEGFR-2 and VEGFR-3.[8] VEGFR-2 is thought to be the principal mediator of angiogenesis, whereas VEGFR-3 is crucial for development and growth of lymphatic and blood vessels.[8]

Integrins Expression

Integrins are a family of heterodimeric transmembrane glycoproteins mediating cell–cell and cell–ECM connections. The integrin family consists of eight β and 18 α subunits that assemble as heterodimers to form 24 distinct integrins[15] (Fig. 2). The main ligands for integrins in the extracellular space are extracellular matrix proteins, such as laminin and collagen, as well as cellular counter-receptors. Integrins are linked to the cytoskeleton through their cytoplasmic domains. Integrins modulate the cytoskeleton via various submembrane adaptor proteins and kinases.[16] Integrins transduce signals across the plasma membrane in both directions; integrin binding to its ligands requires its activation by inside-out signals. Conversely, integrin ligation triggers outside-in signals that regulate different aspects of cell behavior, including cell

survival, control of transcription, cell proliferation, cell motility, and cytoskeletal organization.[15]

Many integrins, including αvβ3, α5β1, αIIbβ3, αvβ6, and α3β1, recognize the tripeptide Arg–Gly–Asp (RGD) in their ligands.[17] Sequences flanking the RGD peptide are also important for integrin selectivity.[18] Other integrins recognize alternative short peptide sequences; for example, integrin α4β1 recognizes Glu-Ile-Leu-Asp-Val (EILDV) and Arg-Glu-Asp-Val (REDV) in the alternatively spliced fibronectin domain known as IIICS.[19] Some integrins, such as α4β1, can also bind cell surface receptors, such as Vascular Cell Adhesion Molecule-1 (VCAM-1), to promote cell–cell adhesion.[20]

Upon activation, integrins bind to their matrix ligands, resulting in integrin clustering. Structural and signaling proteins are recruited into these newly formed integrin clusters, allowing both structure-dependent signal regulation and signaling-induced changes in adhesion complex structure. Focal adhesions are highly organized protein scaffolds which link integrins and actin microfilaments termed stress fibers. FAK expression is ubiquitous and FAK is activated by numerous integrins, including β1, β2, and β3 integrins, suggesting FAK activation is a common adhesion-dependent signal. Upon localization to integrin clusters, FAK becomes autophosphorylated on Tyr397 which activates a number of downstream targets through recruitment of SH2 domain-containing proteins such as c-Src, phosphatidyl inositol 3-kinase, and Shc.[21–23]

Cell migration and invasion are crucial processes in a variety of physiological and pathological conditions. They have been identified as prerequisites for reproduction, growth, and development.[24] In addition, migration and invasion perform critical functions not only in normal homeostasis including proper wound healing and immune system function but also in pathological conditions including tumor progression via angiogenesis and metastasis. These processes are controlled by a variety of internal and external signals via complex signal transduction cascades. A variety of molecules in focal adhesions and the actin cytoskeleton are involved in cell migration in a coordinated manner.[25] For the process of cell migration, the assembly and disassembly of cell adhesion sites occur simultaneously at both the front and rear edge of a cell. The invasion process requires the proteolytic degradation of the ECM by several proteases, including matrix metalloproteinases (MMPs), plasminogen activators, and serine proteases.

Because integrins serve as transmembrane linkers between their extracellular ligands and the cytoskeleton, they have the capacity to influence cell migration during embryogenesis, angiogenesis, wound healing, immune and nonimmune defense mechanisms, hemostasis, and oncogenic transformation.

Role of Integrins in Angiogenesis

The formation of new blood vessels depends on a finely tuned interaction between cells, extracellular matrix molecules, growth factors and proteases. The largest body of data has linked αvβ3 and αvβ5 integrins (both receptors for vitronectin and other extracellular matrix molecules) with blood vessel development.[26] Particular attention has been paid to the role of αvβ3 integrin in angiogenesis as it is prominent on proliferating vascular endothelial cells. In particular, proliferating endothelial cells express αvβ3, a key molecule for capillary formation.[26,27] It serves the endothelial cell as a cell surface receptor for several extracellular matrix proteins containing the RGD tripeptide motive. The integrin αvβ3 consists of a complex of two transmembrane glycoproteins that mediate signal transfer from the extracellular matrix to the cytoskeleton. It is involved in intracellular signal transduction and supports migration and survival of endothelial cells. Under steady-state conditions, integrin αvβ3 is not widely expressed. It is upregulated on cytokine-activated endothelial as well as on vascular cells within

malignant tumors.[26–29] Blockade of αvβ3 integrin with monoclonal antibodies or low-molecular-weight antagonists inhibits blood vessel formation in a variety of *in vivo* models, including tumor angiogenesis and neovascularization during oxygen-induced retinopathy.[26, 29–32] A single small-molecule inhibitor of both αvβ3 and αvβ5 integrins inhibited tumor angiogenesis in animal models.[32] Taken together, these inhibition data suggest critical roles for αvβ3 in angiogenesis, and highlight its potential as a potential target in anti-angiogenic therapy. In fact, several αvβ3-integrin antagonists are presently in clinical trials.[33]

In contrast with these inhibitor studies, genetic studies have suggested that integrin αvβ3 is not required for angiogenesis. For example, some mice lacking αv integrins exhibit extensive developmental angiogenesis. Most αv-null embryonic mice develop normally until embryonic day 9.5 whereupon 80% of mice exhibit placental crises; approximately 20% of αv-null mice survive to birth but die just after birth with extensive brain hemorrhages.[34] Similarly, only 50% of β3-null mice are viable and fertile; in these mice, developmental angiogenesis, including postnatal neovascularization of the retina, appears to be β3 independent.[35] While half of integrin β3-null mice survive embryogenesis, the other half die in utero, exhibiting intrauterine bleeding or defective placental development.[35] Surprisingly, β3-null mice show upregulated tumor angiogenesis compared with normal mice, with strongly enhanced VEGFR2 expression and signaling.[36,37] Additionally, male mice lacking β3 integrin have coronary capillaries of irregular endothelial thickness, with endothelial protrusions into the lumen, and expanded cytoplasmic vacuoles.[38] These defective coronary vessels can be normalized by administration of inhibitors of VEGF or Flk-1, suggesting that enhanced VEGF signaling may compensate for the loss of β3 integrin.[38] These results suggest that compensatory VEGFR2 signaling changes may play a role in the survival of β3-deficient animals.

In contrast to β3-null mice, integrin β5-null mice are viable and fertile and have no defects in wound healing.[39] Viable β5-null mice were born at the expected Mendelian frequency from heterozygous intercrosses, demonstrating that the β5 subunit is not required for mouse embryonic development.

Thus, studies of integrin antagonists suggest that αv integrins promote angiogenesis, while genetic deletions suggest that αv integrins are not required for angiogenesis. New evidence suggests that is that animals lacking αv integrins develop compensatory changes in VEGF signaling that permit angiogenesis to occur during embryogenesis. For example, knockin mutant animals expressing the point mutations Y747F and Y759F in the integrin β3 cytoplasmic tail developed normally, but exhibit reduced growth factor and tumor induced angiogenesis *in vivo*.[40] Mutant endothelial cells exhibit impaired adhesion, spreading, migration, and tube formation, as well as impaired complex formation between VEGF receptor-2 and β3 integrin.[40] These results provide genetic evidence that integrin β3 plays an important role in promoting angiogenesis.[40] Thus, integrin αvβ3 plays an important role in angiogenesis and loss of expression of this integrin in development can be partially compensated for by upregulation of other angiogenesis signaling pathways. Importantly, antagonists of αv integrins are currently in phase I–III clinical trials.[41]

Fibronectin Binding Integrins

Fibronectin is an integrin ligand that plays an essential role in cell adhesion and migration during angiogenesis. Fibronectin is secreted as a soluble homodimeric protein of 250 kDa (plasma fibronectin) that forms insoluble fibrillar networks in ECM (cellular fibronectin). It is composed of three types of repeating modules, fibronectin type I, II, and III. Fibronectin is essential for developmental angiogenesis as deletion of all fibronectin isoforms is early embryonic lethal, with yolk sac and other mesodermal tissue defects.[42] Deletion of only EIIIA and EIIIB alternatively spliced variants is also embryonic lethal with severe vascular defects

that suppress placentation, yolk sac vessel formation, and heart formation.[43] Thus fibronectin plays a key role in angiogenesis, as do many of its receptors, the β1 integrins.

Capillary maturation is associated with a developmental switch in the expression of ECM proteins and endothelial cell β integrins.[44] Integrin β1 is required for early development, as well as for blood vessel development, as loss of β1 causes early embryonic lethality and inhibits vessel formation in teratomas and embryoid bodies.[45–47] Mice with an endothelial cell specific deletion of β1 integrin (Tie2Cre floxed β1) also die by E10.5 with severe vascular defects.[48]

Genetic ablation of the major fibronectin-binding integrin, integrin α5, leads to severe developmental abnormalities including vascular abnormalities.[49] In combination with its extracellular ligand fibronectin, which is able to provide proliferative signals to vascular cells, α5β1 integrin is also upregulated in tumor blood vessels and plays a role in tumor angiogenesis and growth.[50,51] Very recent data have shown that the integrin α5β1 is also involved in choroidal neovascularization in a laser injury model in mice. Integrin α5β1 inhibition caused prevention and regression of choroidal neovascularization.[52] Importantly, antagonists of α5β1 are currently in clinical trials for cancer therapy.[53]

Integrin α4β1 is another fibronectin receptor that is best known as a lymphocyte integrin that mediates adhesion of circulating lymphocytes to VCAM-1 expressed on activated endothelia in inflamed tissues, thereby promoting extravasation of lymphocytes into inflamed tissue.[54] Integrin α4β1 and VCAM have been shown to regulate embryonic development, as loss of either integrin alpha 4 or VCAM genes cause embryonic lethality by E11.5–E12.5 from a failure of the endocardium to fuse with the myocardium and a failure of the chorion to fuse with the allantois.[55,56] In addition, loss of either gene results in abortive coronary artery formation, which results in cardiac hemorrhage. Moreover, both α4β1 and VCAM-1 promote tumor angiogenesis;[57] interactions of these molecules are required for tumor angiogenesis as they promote the adhesion of endothelial and mural cells during tumor vessel formation.[57]

Integrin α9β1 is also a fibronectin-binding integrin implicated in angiogenesis.[58] Expression of α9β1 integrin is widely distributed on many cell types including epithelial cells, muscle cells, neutrophils, and endothelial cells. Blockade of α9β1 inhibited VEGF-A-induced angiogenesis.[59–61] However, integrin α9-null mice do not exhibit obvious defects in blood vessel development but develop fatal bilateral chylothorax, an accumulation of fat in the pleural space due to inadequate lymph vessel development or function. These mice die of respiratory failure with defects in lymphatic vessels development.[39]

Additional ECM-binding integrins that play critical roles in angiogenesis include α1β1 and α2β1 which bind laminin and collagen. In normal animals, VEGF-A treatment upregulates expression of both α1β1 and α2β1 on vascular endothelial cells.[62,63] Function-blocking antibodies directed against both integrins reduced angiogenesis *in vitro*, VEGF-A induced angiogenesis *in vivo* and reduced tumor growth, angiogenesis, and lymphangiogenesis.[62–66] Integrin α1 null mice demonstrate decreased tumor growth and angiogenesis, a finding consistent with the α1β1 integrin serving a proangiogenic function.[67,68] In contrast, integrin α2 null mice sometimes exhibited increased tumor angiogenesis.[69] Mice null for α2 integrin had enhanced B16F10 melanoma, but not Lewis lung carcinoma, tumor growth, and angiogenesis. Further analysis revealed that α2β1 null mice upregulated VEGFR1 expression and function on endothelial cells, thereby promoting a growth advantage to tumor cells that produced ligands for VEGFR1. In fact, B16F10 melanoma cells express high levels of the VEGFR1 binding growth factor PLGF, while Lewis Lung carcinoma cells expressed low levels of PLGF.[69] Integrins α1β1 and α2β1 appear to play important roles in tumor angiogenesis.

The integrin α6 can form heterodimers with both β1 and β4 subunits. Integrin α6β1 can bind many ECM proteins such as laminin, thrombospondin, and CYR61, whereas α6β4 primarily

binds laminin.[70,71] Integrin α6β1 is expressed at high levels in capillary endothelial cells *in vivo*.[70] Antibody inhibitors of α6 integrin inhibit endothelial cell tube formation *in vitro*, suggesting a role for α6 in angiogenesis.[70] Endothelial cell migration and tube formation were also blocked by downregulation of α6 expression in brain microvascular endothelial cells with siRNA.[70] Importantly, the β4 integrin subunit and its ligand laminin, is expressed by human and murine tumor endothelium.[71] Mice with genetic deletions of the β4 or the α6 subunit do not exhibit overt vascular defects but die immediately after birth, in part due to severe skin blistering caused by passage through the birth canal,[72–74]

In stably adherent cells, the β4 integrin mediates hemidesmosome assembly[74]. However, hemidesmosomes do not form in growth factor stimulated cells; instead, the β4 subunit cytoplasmic tail is tyrosine phosphorylated in response to receptor tyrosine kinase activation of the Src family kinases. Upon phosphorylation of Tyr(1440) and Tyr(1422), the β4 subunit interacts with the SH2 domain of Shc, promoting Raf-ERK and Rac-JNK signaling and immediately early gene expression[75]. Mice with a targeted deletion of the C-terminal portion of the β4 subunit cytoplasmic tail (Δ1355) develop normally, but adult mice show reduced angiogenesis in response to bFGF and VEGF in tumors. Spontaneous tumor growth in these animals was also suppressed[71]. These studies imply that integrin α6β4 is a novel target for anti-angiogenic therapies.

Integrin α6β1 is also expressed on endothelium; its expression can be confirmed by immunoprecipitation[70]. As α6 integrin antagonists and siRNA constructs inhibit angiogenesis, it is likely that integrin α6β1promotes angiogenesis. However, as these agents can block the function of both integrins α6β1 and α6β4, it is not yet clear what role integrin α6β1 plays in tumor angiogenesis.

Taken together, integrins can be considered as useful targets for the treatment of angiogenesis associated with cancer.

Role of Integrins in Lymphangiogenesis

In contrast to the role of integrins in hemangiogenesis, to date less is known about the expression of integrins on lymphatic endothelial cells (LECs) *in vivo* and their functional relevance in lymphangiogenesis. Substantial evidence supports a role for integrin α9 during the development of the lymphatic system. Integrin α9-null mice died 6–12 days after birth with accumulation of fat in the pleural space (chylothorax). Chylothorax is often indicative of inadequate lymph vessel development or function. The presence of edema and extravascular lymphocytes surrounding the thoracic duct and other lymphatic vessels suggested a defect in lymphatic development.[39] Nevertheless, the molecular mechanisms underlying the role of α9β1 in lymphatic development remain unexplained.

Other studies have shown that integrins α1β1 and α2β1 are expressed on lymphatic endothelium in healing wounds in response to VEGF-A. Inhibition of these integrins blocked lymphangiogenesis in these wounds.[76] More recently, the integrin α1 has been found to be expressed on lymphatic endothelial cells isolated from patient with lymphangioma.[77]

One fibronectin receptor, the integrin α4β1 is expressed on tumor and growth factor-induced lymphatic endothelium, and antagonists of this integrin can block lymphangiogenesis and tumor metastasis.[78] In contrast, αv integrins appear to play little or no role in lymphangiogenesis and integrin α5β1 appears to play no role in tumor lymphangiogenesis.[78] Integrin α5β1 is expressed by a subpopulation of lymphatic vessels in the inflamed cornea, and small molecule antagonists of this integrin inhibited inflammatory lymphangiogenesis.[79]

Tumor lymphangiogenesis and its role in tumor metastasis are of particular importance for the understanding of cancer progression. Several integrins appear to play important roles in lymphangiogenesis, yet the profile of integrins regulating lymphangiogenesis are distinct from those regulating angiogenesis. Importantly, antagonists of these integrins may be useful in preventing tumor metastasis by blocking lymphangiogenesis.

Therapeutic Applications

Preclinical studies have suggested that antagonists of several integrins might be useful to suppress tumor angiogenesis and growth, either alone or in combination with current cancer therapeutics.

Of the several integrin antagonists undergoing clinical evaluation for cancer treatment, all have proven nontoxic, including Abegrin (Medi-522), a humanized anti- αvβ3 antibody,[33, 80–82] CNTO95, a human αvβ3/αvβ5 antibody, Volociximab, a chimeric mouse/human anti-α5β1 antibody, Cilengitide, a cyclic peptide inhibitor of integrins αvβ3/αvβ5 and ATN161, a non-RGD based peptide inhibitor of α5β1. These agents are likely nontoxic because the targeted integrins are only expressed or activated in remodeling tissues such as tumors.

Abegrin, or MEDI-522, was the first anti-integrin therapeutic to be tested in clinical trials for cancer.[33, 80–82] It is a humanized version of the anti-integrin αvβ3 monoclonal antibody LM609, which has been shown to block tumor angiogenesis by inducing apoptosis in newly formed endothelial cells. A recent study in patients showed that MEDI-522 showed functional efficacy by reducing focal adhesion kinase activity in patients blood vessels.[82] Based on these results, Phase III cancer clinical trials are in the planning stages.

On the basis of preclinical studies showing both integrins αvβ3 and αvβ5 regulate angiogenesis, a human monoclonal antibody directed against both αvβ3 and αvβ5 integrins, CNTO 95, was developed by Centocor.[83,84] CNTO 95 reduced angiogenesis and tumor growth in human melanoma xenografts in nude mice and rats.[83] CNTO95 is now under evaluation in Phase I/II clinical trials for the treatment of melanoma.[84] As CNTO95 inhibits both integrins αvβ3 and αvβ5, two of the integrins that promote tumor angiogenesis, it may have wide-spread clinical utility. Additionally, most carcinoma cells express integrin αvβ5, which has been shown to promote tumor cell invasion.[85] Targeting the alpha v integrins may thus block both tumor cell invasion and metastasis and tumor angiogenesis.

For these reasons, a cyclic RGD-peptide antagonist of αvβ3/αvβ5, Cilengitide (EMD 121974) has been developed as a cancer therapeutic. This drug was evaluated in Phase I/IIa clinical trials for glioblastoma and significantly enhanced progression free survival was observed.[86] On this basis, as of 2007, E. Merck was planning to evaluate Cilengitide in Phase III trials for glioblastoma. Cilengitide is currently in phase II trials for glioblastoma, non-small cell lung cancer, melanoma, and pancreatic cancer.[87,88] Therefore, three distinct alpha v integrin targeting drugs offer promise as cancer therapeutics.

Since beta 1 integrins also play significant roles in angiogenesis, targeting these integrins in addition to alpha v integrins may be provide useful benefit in suppressing angiogenesis and tumor growth. A chimeric mouse/human anti-α5β1 antibody, M200 (volociximab), was evaluated in Phase II trials in combination with DTIC, the antibody was well-tolerated and anti-tumor activity was noted in 62% of patients.[53]

Another inhibitor of integrin α5β1, the peptide ATN-161, is also developed in clinical trials. In animal models of colon cancer, ATN-161 reduced metastases and improved survival when combined with chemotherapy.[89]

However, as many integrins can promote angiogenesis, it is not yet clear whether targeting one or more than one will have the most significant impact on tumor angiogenesis and growth. It is likely also that integrin antagonists may be combined with other angiogenesis inhibitors such as VEGF inhibitors like Avastin.

Conclusions/Perspectives

During adulthood, most blood vessels remain quiescent, and angiogenesis occurs only in the cycling ovary and in the placenta during pregnancy. Additionally, lymphangiogenesis is reactivated during wound healing and repair. But in many disorders, both angiogenesis and lymphangiogenesis processes are activated. These include tumor growth and metastasis, as well as ocular and inflammatory diseases.

Changes in integrin expression or function are directly involved in angiogenesis, tumor growth, and metastasis, making these receptors promising targets for novel anticancer therapies. Various integrins are highly expressed on angiogenic, proliferating tumor blood vessels and are expressed at a much lower level on normal vessels. Moreover, agents targeting integrin receptors are now in clinical development for treating solid tumors. Preclinical evidence indicates that vascular integrins are potentially relevant targets for anti-angiogenic therapies. As few side effects are associated with integrin inhibitors, use of these new drugs in combination with chemotherapy may prove an effective means to inhibit tumor associated angiogenesis and lymphangiogenesis.

Acknowledgments

This work was supported by NCI/NIH Grants CA83133, CA98048, and CA126820 to Judith A. Varner and a postdoctoral fellowship from the California Breast Cancer Research Program to Barbara Garmy-Susini.

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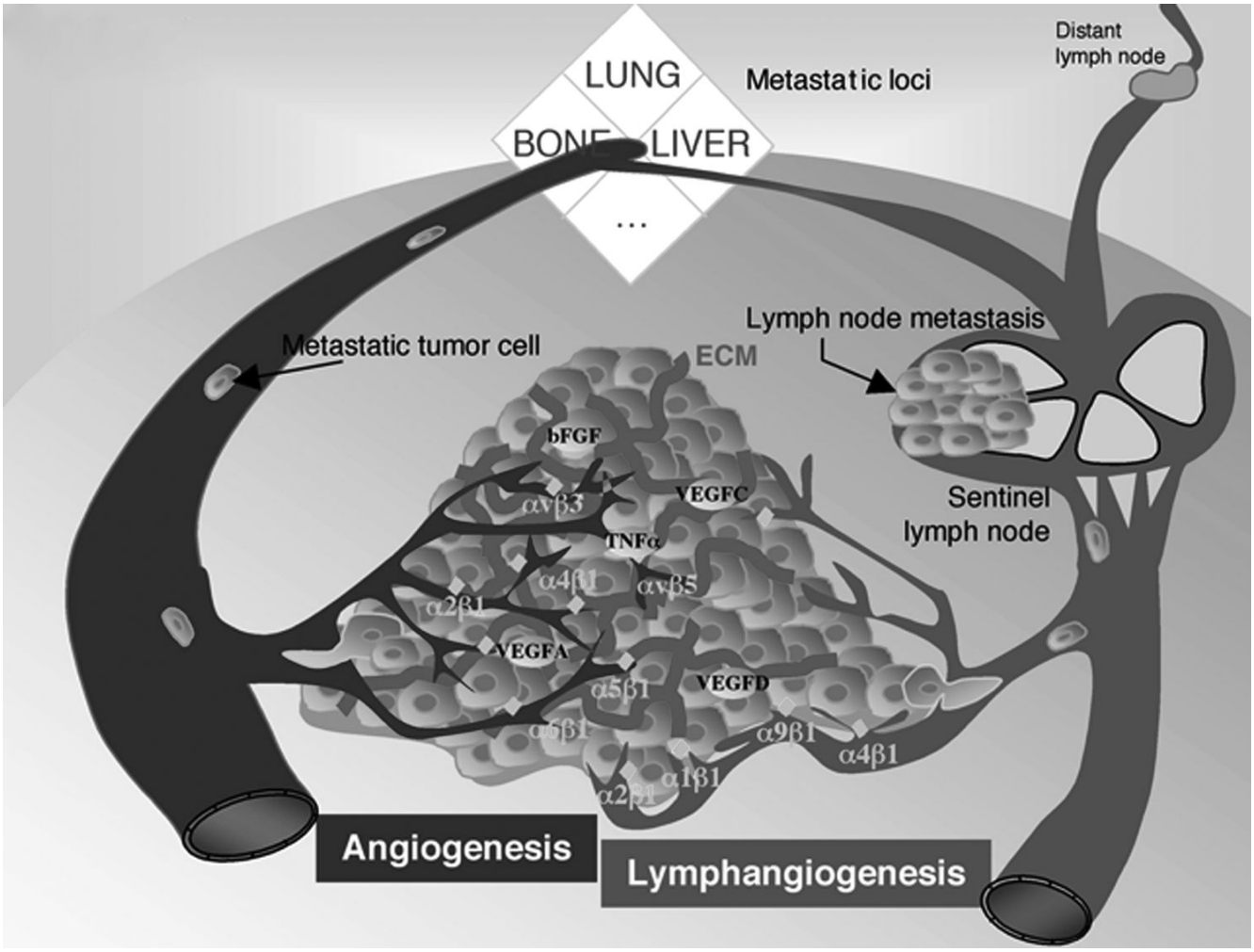

FIG. 1.

Mechanisms regulating angiogenesis and lymphangiogenesis. Tumor cells near pre-existing blood vessels secrete growth factors and chemokines such as VEGF-A, bFGF, and TNFα that stimulate quiescent vascular endothelium to enter the cell cycle. Tumors also secrete factors such as VEGF-C, VEGFD, or VEGF-A that stimulate the growth of new lymphatic vessels in the peritumoral space. These growth factors activate or upregulate expression of integrins such as α1β1, α2β1, α4β1, α5β1, and αvβ3 on blood vessels and α4β1, α9β1, and α1β1 on lymphatic vessels. Tumor derived VEGF-C also promotes new lymphatic vessel growth in draining lymph nodes. These integrins then promote endothelial cell migration and survival during invasion of tumor tissue, resulting in the creation of new vessels sprouts. The new blood vessels promote tumor growth by removing waste products and providing nutrients. These new blood and lymphatic vessels also provide an avenue for tumor metastasis. Lymphangiogenesis promotes metastasis to lymph nodes and, sometimes, more distant tissues such as lung, whereas angiogenesis promotes metastasis to local and distant sites, such as lung.

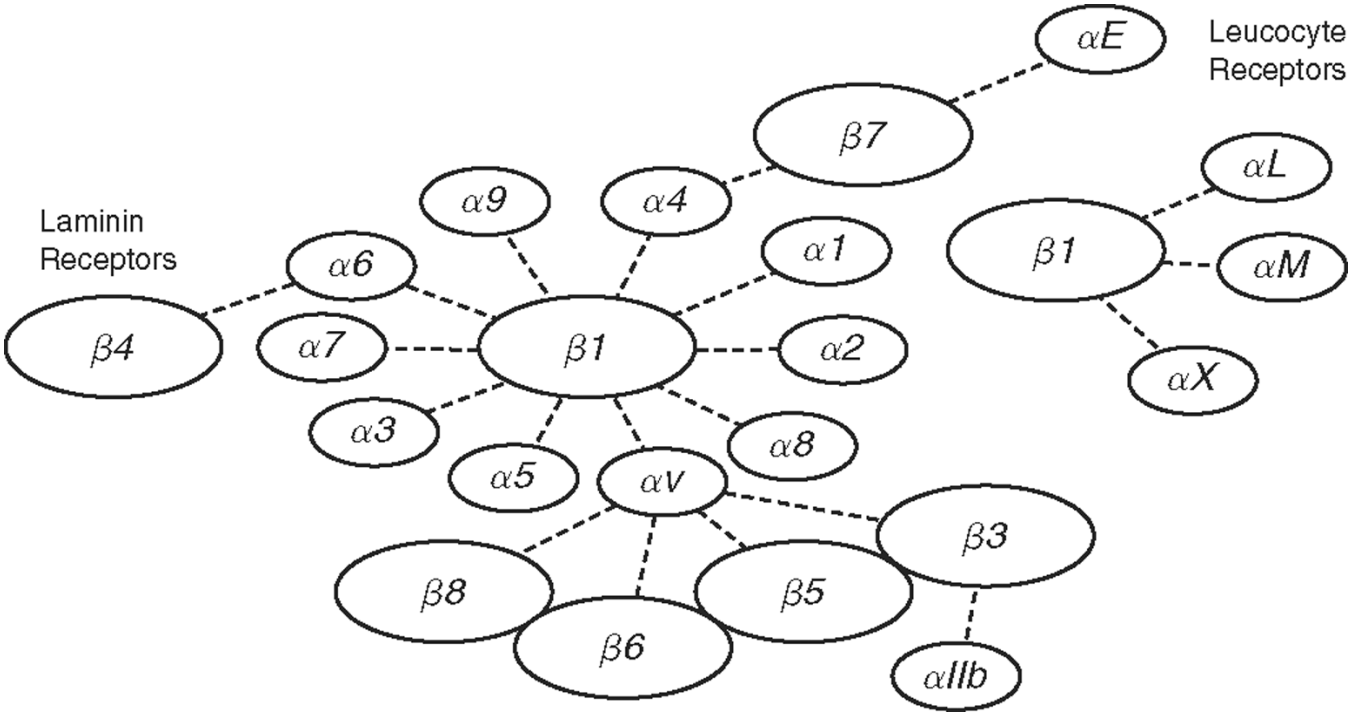

FIG. 2.

Integrin family of adhesion receptors. Each integrin receptor heterodimer binds a specific set of endogenous ligands, which may include ligands in the ECM, soluble ligands, and ligands on other cell surfaces. Integrins are divalent cation-dependent heterodimeric membrane glycoproteins comprised of noncovalently associated α and β subunits. Each integrin subunit consists of an extracellular domain, a single transmembrane region, and a short (approximately 30 to 40 amino acids) cytoplasmic region. Upon ligand binding, a series of intracellular signaling events is initiated. These pathways are associated with enhanced cell proliferation, migration, and survival.