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Integrins in wound healing, fibrosis and tumor stroma: High potential targets for therapeutics and drug delivery☆

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ABSTRACT

Wound healing is a complex process, which ultimately leads to fibrosis if not repaired well. Pathologically very similar to fibrosis is the tumor stroma, found in several solid tumors which are regarded as wounds that do not heal. Integrins are heterodimeric surface receptors which control various physiological cellular functions. Additionally, integrins also sense ECM-induced extracellular changes during pathological events, leading to cellular responses, which influence ECM remodeling. The purpose and scope of this review is to introduce integrins as key targets for therapeutics and drug delivery within the scope of wound healing, fibrosis and the tumor stroma. This review provides a general introduction to the biology of integrins including their types, ligands, means of signaling and interaction with growth factor receptors. Furthermore, we highlight integrins as key targets for therapeutics and drug delivery, based on their biological role, expression pattern within human tissues and at cellular level. Next, therapeutic approaches targeting integrins, with a focus on clinical studies, and targeted drug delivery strategies based on ligands are described.

Contents

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1. Introduction

Wound healing is a complex process, which if not repaired leads to scar formation so-called fibrosis. Fibrosis, a hallmark of an excessive extracellular matrix (ECM) deposition, accounts for about 45% of lethalities in the modern world [1]. In general, fibrotic diseases are caused by chronic tissue injury, resulting in chronic inflammation and fibrosis which leads to destruction of the normal tissue architecture and ultimately organ failure. Currently, there are no effective treatment opportunities for tissue fibrosis and therefore there is a desperate need for effective anti-fibrotic therapies. In addition, tumors are regarded as "wounds that do not heal" due to extensive fibrosis within tumors. Fibrosis and tumor share a strikingly similar cellular and microenvironmental reactivity. Several tumor types undergo a fibrotic reaction so-called desmoplasia or tumor stroma. The tumor stroma has been shown to strongly support the tumor growth by many means and therefore these tumors are referred to as fibrosis-driven tumors [2].

Tissue fibrogenesis is a complex process orchestrated by a bidirectional crosstalk between the different cell types including inflammatory cells, epithelial cells, myofibroblast and ECM in response to the wound healing process [3]. Cell fate within fibrotic tissues is profoundly affected by the highly dynamic environment of the pericellular ECM mainly produced by myofibroblasts [4]. During fibrosis, integrins, a family of transmembrane receptors, mediate various cell-matrix and cell-cell interactions. Integrins facilitate communication between the ECM, non-parenchymal cells including inflammatory cells, fibroblasts, and parenchymal cells, and by these interactions, integrins are directly involved in the initiation and progression of tissue fibrosis [4]. Therefore, integrins represent highly interesting therapeutic targets.

Within this review, we provide a general introduction of integrins and integrin-mediated signaling, an overview of integrin expression in fibrosis-related cell types, and interaction between integrins and growth factor receptors. The next section describes the role of integrins in wound healing, fibrosis-driven tumor, tumor metastasis and fibrosis. Finally, the last two sections are focused on the novel therapies based on integrin inhibition, including clinical developments, and drug delivery strategies to target integrins.

2. Integrin receptors

2.1. Integrin heterodimers and ligand specificity

Integrins are a family of heterodimeric cell surface receptors, each consisting of one α and one β subunit. Overall, there are 18 α and 8 β subunits that combine to form heterodimers. So far 24 different functional heterodimeric integrin receptors have been identified. Each integrin receptor specifically binds to one or more ligands. Their specific ligand binding ability enables cells to connect with its surrounding extracellular matrix (ECM), thereby enabling cell motility and invasion. Integrins possess a physical connection with the inside and the outside of a cell, which allows for bidirectional sensing of signals. With this mechanism, integrins ultimately control cytoskeleton organization, thereby directly affecting essential cellular functions such as cell adhesion, migration, proliferation, survival and differentiation [5]. The local expression pattern of both integrins and their ligands controls the response of a cell to its microenvironment, as every individual integrin heterodimer is capable to bind multiple ligands and also a ligand may bind to multiple integrin heterodimers [5].

In addition to controlling a range of physiological functions, integrins also sense ECM-induced extracellular changes during pathological events such as fibrosis, cancer and wound healing, leading to cellular responses, which influence ECM remodeling [5]. Next to binding ECM components, integrins are also capable of participating in cell-cell adhesions, for which they bind to counter receptors on adjacent cells such as ADAMs (A Disintergins And Matrix metalloproteinases (MMPs)), thereby promoting matrix remodeling [6]; as well as immunoglobulin-type receptors such as intracellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs) which are expressed on leukocytes and endothelial cells [7].

Integrins can be classified into five different integrin subfamilies (Table 1) [6]. Integrin α1β1, α2β1, α10β1, α11β1, belong to the β1 containing collagen receptors [6]. The integrins α5β1, α8β1, αvβ1, αvβ3, αvβ5, αvβ6, αvβ8 and αIIbβ1, belong to the RGD (arginine-glycine-aspartic acid)-binding integrins capable of binding to the ECM and plasma proteins such as fibronectin, vitronectin, fibrinogen and thrombospondin [6,8]. The integrins α3β1, α6β1, α7β1 and α6β4 are laminin receptors that mediate cell adhesion to the basement membranes of various tissues [6]. The α4β1, α9β1, α4β7 integrin family also binds to fibronectin but in a RGD-independent manner via the adhesive sequences EILDV and REDV [6,8]. Additionally, integrin α4β1 and α4β7 are also able to bind counter receptors in other cells e.g. intercellular adhesion molecules [6]. Integrins αDβ2, αLβ2, αMβ2, αXβ2 and αEβ2 belong to the leukocyte integrin subgroup, binding to receptors such as intracellular adhesion molecules (ICAMs) and plasma proteins such as complement component C3b and C4b [6].

Table 1
Integrin heterodimer subfamilies comprised of 24 integrin receptors and their respective ligands.

Integrin receptor subfamilies	Integrin type
Collagen receptors	α1β1, α2β1, α10β1, α11β1
Fibronectin, vitronectin, fibrinogen and thrombospondin receptors (RGD binding)	α5β1, α8β1, αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, αIIbβ1
Laminin receptors	α3β1, α6β1, α7β1, α6β4
Fibronectin receptors (non-RGD binding)	α4β1, α9β1, α4β7
Leukocyte receptors	αDβ2, αLβ2, αMβ2, αXβ2, αEβ2, α4β1, α4β7

2.2. Integrin signaling

During interactions of integrins with ligands of the surrounding ECM, integrins undergo a conformational change and cluster in the plane of the cell-membrane [8]. This change in conformation activates integrins to a high avidity state. Within this state, integrins recruit various signaling and adaptor molecules to form focal adhesions [8]. The composition of these focal adhesions varies dependent on whether these contacts are formed in a two-dimensional or three-dimensional environment [9]. While lacking kinase activity by themselves, clustered integrins are capable of recruiting and activating kinases such as focal adhesion kinase (FAK), Src family kinases (SFKs) and scaffold molecules such as p130CRK-associated substrate (p130CAS or BCAR1) [8].

Next to activating kinases, integrins can also connect the ECM to the actin cytoskeleton by recruiting proteins including talin, paxillin, α-actinin, tensin and vinculin [8]. Furthermore, several scaffolding and signaling functions required for integrin-mediated effects on cell migration and survival are controlled by the integrin-linked kinase (ILK), PINCH and parvin. The ILK-PINCH-parvin (IPP) ternary complex functions as an essential signaling platform that regulates various scaffolding and

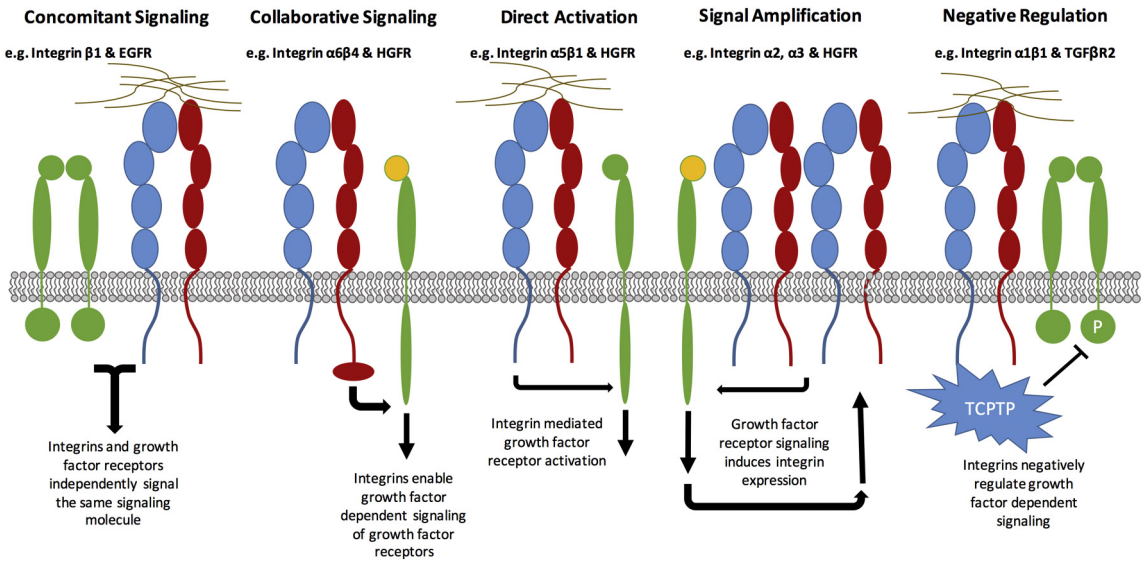

Fig. 1. Schematic representation and description of the distinct mechanisms by which integrins and growth factor receptors regulate the activation of signaling pathways within the cell. During concominant signaling, integrins together with growth factor receptors, signal independently to trigger the same signaling molecule. Thereby, integrins gather a platform of signaling proteins, which facilitate growth factor receptors signaling. During direct activation, integrins activate growth factor receptor signaling independent of growth factors. In collaborative signaling, integrin receptors create a permissive environment which enables growth factor receptors to interact with downstream signaling molecules. Growth factor receptor signaling triggers increased integrin expression, which can further induce growth factor receptor signaling. Integrin interaction with the ECM can cause negative regulation of growth factor receptor signaling through phosphatase activation and recruitment of, for example, T cell protein tyrosine phosphatase (TCPTP). Integrins that are involved in the different signaling mechanism are stated as examples. The cooperation between integrins and growth factor receptors has been reviewed in more detail by Ivaska *et al.* [13].

signaling functions which enable integrin-mediated effects on cell migration and survival [10]. Moreover, integrins function in tumor cells might be regulated by integrin recruitment to microdomains by tetraspanin [8]. Regulation and activation of microdomains and other focal adhesion proteins influence cell adhesion and migration on the ECM. Many of these molecules are investigated as promising therapeutic targets [8]. In some cases, integrin function is based on its ligand binding affinity [8]. The affinity and activation of an integrin receptor can be induced by ligand-mediated integrin clustering or increased intracellular signaling driven by molecules such as GTPase RAP1A [11]. Therefore, signaling which is induced by oncogenes or growth factor receptors might influence integrin affinity and function [8].

2.3. Integrins and growth factor receptor interactions

Integrins and growth factor receptors play an important role for signal integration [12]. Crosstalk between integrins and growth factor receptors have been described for the TGFβ receptor, epidermal growth factor receptor (EGFR), Met receptor (hepatocyte growth factor receptor (HGFR) superfamily), platelet derived growth factor receptor (PDGFR), insulin receptor and vascular endothelial growth factor receptor (VEGFR) [12]. There are various different classes of signal integration between different integrins and growth factor receptors [13]. In the following, we describe the five classes of signal coordination (i) concominant signaling, (ii) collaborative signaling, (iii) direct activation and (iv) amplification of signaling and (v) negative regulation (Fig. 1) [13].

(i) Concomitant signaling

During concomitant signaling, integrins together with growth factor receptors signal independently to trigger the same signaling molecule (Fig. 1). Pathways which are affected by concomitant signaling include Ras-MAPK (mitogen-activated protein kinase), PI3K-Akt (PI3K (phosphatidylinositol 3-kinase)) and Akt (Protein Kinase B), and Rho [12–15]. As an example Akt can be activated by integrins and growth factor receptors in a PI3K-dependent manner via distinct mechanisms [13]. Phosphorylation of Akt at Ser473 and Thr308 and of Akt kinase activity is induced by integrin β1 independently of EGFR signaling, while epithelial growth factor (EGF) induces Akt activity via the Fak and Src independent of cell adhesion [13].

(ii) Collaborative signaling

Collaborative signaling is very similar to concomitant signaling in the way that cells require integrin-mediated adhesion to proceed through the cell cycle and respond to growth factors, since growth factor receptor signaling is inefficient in the absence of cell adhesion [13]. During collaborative signaling, integrin receptors create a permissive environment in which growth factor receptors can interact with downstream signaling molecules (Fig. 1) [16]. The difference between concomitant and collaborative signaling is that during collaborative signaling the receptor signals are spatially and temporally controlled while in concomitant both integrins and growth factor receptors work independently [13]. An example for this type of signaling is that cells which only express Met in the absence of integrin α6β4 no-longer respond to hepatocyte growth factor (HGF) showing the collaboration between integrin α6β4 and the Met receptor (HGFR) [17].

(iii) Direct activation

During direct activation of growth factor receptors, integrins induce growth factor phosphorylation in absence of the corresponding growth factor (Fig. 1). This ligand-independent activation process has been shown for the growth factor receptors EGFR, Ron (Recepteur d'Origine nantais, member of HGFR superfamily), VEGFR, IGFR (insulin-like growth factor receptor) and PDGFR [18–25]. An example for direct activation is the ability of integrin αvβ3 to activate VEGFR-2, IGFR-1 and PDGFR in a growth factor independent manner [21–26]. Additionally, in macrophages integrin β1 is associated with Ron and the adhesion to collagen or fibronectin results in the phosphorylation of Ron in a Src-dependent manner and binding of integrin α5β1 by fibronectin induces activation of Met [20,26].

(iv) Amplification of signaling

Another form of crosstalk between integrins and growth factor receptors is amplification of signaling. It is based on the ability of growth factors to activate signaling by binding to their corresponding growth factor receptors which can then increase the expression of integrins [13]. This amplification process has for example been shown for HGF, increasing the expression of integrin α2 and α3 [27,28], which could contribute to the amplification of Met signaling in response to HGF via the FAK-Src axis [13].

(v) Negative regulation

As described above, integrins mostly function as positive regulators of growth factor receptor signaling. However, integrin interaction with the ECM can also inhibit growth factor receptor signaling through phosphatase activation and recruitment of, for example, T cell protein tyrosine phosphatase (TCPTP) (Fig. 1) [13]. In renal fibrosis, it has been shown that Integrin α1β1 reduces Smad-dependent profibrotic signaling in kidney duct derived cells by TCPTP-mediated dephosphorylation of TGFβR2 (a variant of the TGFβ receptors II) [29].

2.4. Integrin and growth factor receptor interactions

The following are some examples showing interactions between integrins and growth factor receptors in relation to fibrosis and cancer. Growing evidence suggests that the progression of fibrosis is affected by signaling between integrins, growth factor receptors and cytokine or chemokine receptors. Next to cell adhesion, migration, invasion and survival, integrin crosstalk also affects the host response to fibrosis driven diseases [8].

(i) Interaction with TGFβR

Transforming growth factor beta 1 (TGFβ1), in its secreted form, is one of the main pro-fibrotic cytokines and regulator of fibrosis in multiple organs [3]. Most of the pro-fibrogenic TGFβ1 is secreted and bound to the ECM in its latent form [3]. Conversion of latent TGFβ1 into its active form is an important step that regulates TGFβ1 activity [3]. αv integrins are known for their ability to activate latent TGFβ1 [4]. Evidence for the interaction between TGFβ and integrins came from the structural analysis of the molecule by Ruoslahti and Pierschbacher *et al.* [30], which suggested that TGFβ1 & TGFβ3 bind to integrins based on their linear sequence of arginine, glycine and aspartic acid (RGD), which is known to be crucial for the interaction of many integrins with their respective ligands. The integrins αvβ1, αvβ3, αvβ5, αvβ6 and αvβ8 were identified to bind to the RGD-sequence of the latency associated peptide (LAP) of TGFβ1 and TGFβ3, and are capable to activate latent TGFβ [31–35]. During pulmonary inflammation and fibrosis, TGFβ1 activation is regulated by integrin αvβ6 [36]. Integrin αvβ6 activates TGFβ by inducing a conformational change in the integrin αvβ6-bound latent TGFβ complex which then presents active TGFβ to its receptor on adjacent cells via cell-cell contact [31,36]. Marsh *et al.* [37] showed that integrin αvβ6 dependent activation of TGFβ resulted in the differentiation of human fibroblasts into tumor stroma-associated myofibroblasts. Myofibroblasts are capable to activate TGFβ1 from self-generated deposits in the ECM by means of αvβ5 integrins which transmits the highly contractile forces of these cells to the latent complex of TGFβ1. Additionally, integrin αvβ8 has been shown to activate TGFβ by presenting the latent TGFβ complex to metalloproteinases that cleave the complex, resulting in the release of free TGFβ into the extracellular milieu [36].

Integrin αvβ3 is known to induce EMT in mammary epithelial cells by cooperating with TGFβ via Src-dependent phosphorylation of TGFβ receptor type 2 [38]. Integrin β3 deficiency in mice was shown to correlate with elevated levels of TGFβ receptor 1 and 2, reduced levels of Smad 3, sustained nuclear localization of Smad 2 & 4 and TGFβ1-mediated fibroblast migration [39]. These data indicate that integrin αvβ3 is expressed on platelets, macrophages, endothelial cells and fibroblasts during wound repair and is capable of repressing TGFβ1-mediated signaling [39]. Increased expression of αvβ5 in fibroblasts increases their responsiveness to TGFβ1 by recruiting latent TGFβ1 on the cell surface and stimulating the interaction between αvβ5 and the TGFβ receptor [40].

(ii) Interaction with VEGFR2

During angiogenesis, endothelial cells express integrin αvβ5 that interacts with VEGF receptor 2 (VEGFR2) to promote VEGF-induced angiogenesis via the Ras-ERK pathway [41,42]. Additionally, integrin αvβ5 in cooperation with VEGFR2 causes inflammatory mediators (e.g. tumor necrosis factor) induced resistance of endothelial cells to extrinsic apoptosis, via Src-dependent phosphorylation of Raf Tyr340 and Tyr341 [5]. Mice with genetic knockout of integrin β3 showed an abnormal endothelial cell morphology which was associated with increased VEGF signaling [43]. Integrins also play a major role in the control of neovascularization in wound healing, where they act as co-receptors for the growth factor-receptors VEGF and angiopoietin, and support the assembly of vascular membranes [6].

(iii) Interaction with FGFR

In endothelial cells, cross-talk between integrin αvβ3 and fibroblast growth factor receptor (FGFR) was found to induce angiogenesis downstream of FGF binding [42]. Evidences support that FGFR and integrin αvβ3 cooperate to increase the phosphorylation of Raf Ser 338 and Ser 339 through the PAK (p21-Activated Protein Kinases) pathway, resulting in Raf-ASK1 complex formation in mitochondria, thereby inhibiting the intrinsic apoptosis pathway [8]. Furthermore, knockdown studies in mice have shown that integrin β4 expression correlates with decreased FGF-induced angiogenesis and reduced tumor size via P-ERK and NF-kappaB signaling pathways [44].

Integrin α1β1 negatively regulates EGFR-mediated Rac activation, thereby reducing the production of reactive oxygen species in mesangial cells resulting in attenuation of fibrogenesis in mice [45]. Additionally, other studies have shown that integrin α1β1 also regulates activation of TCPTP, resulting in the inhibition of EGFR and VEGFR2 signaling [46,47].

(iv) Interaction with other growth factor receptors

Integrin β4 was found to functionally collaborate with the Met tyrosine kinase receptor for HGF resulting in increased fibroblast transformation and tumorigenic potential [48]. The expression of insulin-like growth factor 2 (IGF-2) has shown to be stimulated by the expression of integrin subunit α11β1 in stromal fibroblast of non-small-cell lung carcinoma [49].

In primary cultures of hepatic stellate cells, the liver fibrosis promoting connective tissue growth factor, CTGF (or CCN2), was shown to regulate the expression of integrins on hepatic stellate cells (HSCs) and additionally facilitate HSCs adhesion via binding to integrin α5β1, which interacts cooperatively with heparin sulfate proteoglycans or fibronectin [50].

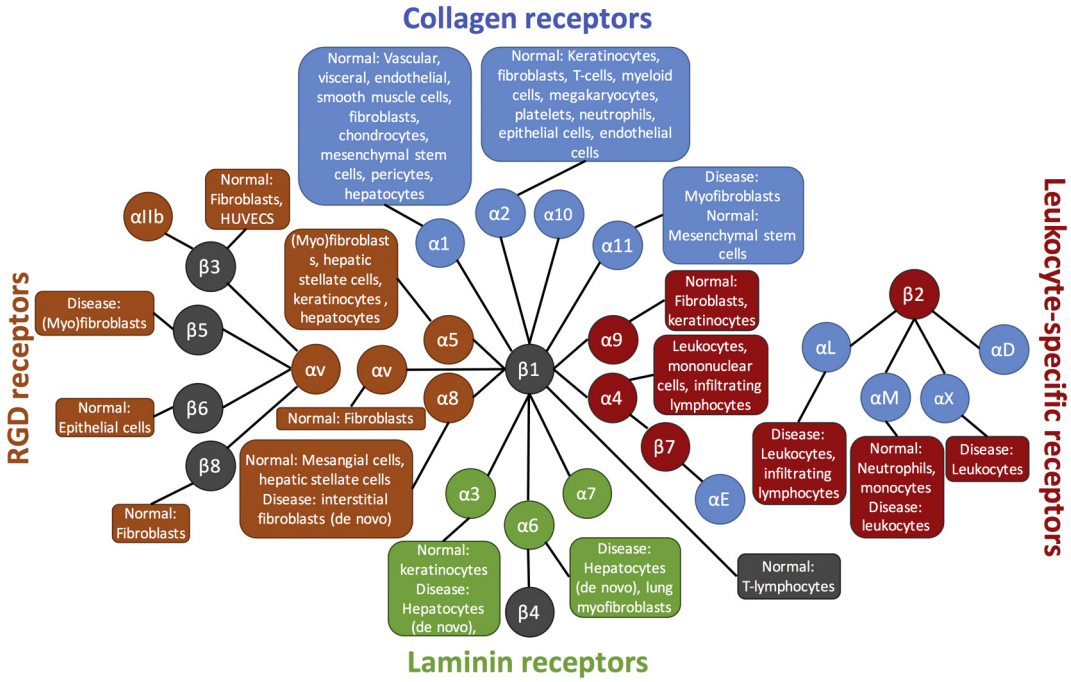

Fig. 2. Schematic representation of the 24 different integrin receptor pairs, including their ligand specificity and cellular expression in fibrosis, tumor stroma and wound healing. The integrins cellular expression has been subdivided into non-pathogenic cells, named "normal", and pathogenic cells, named "disease".

3. Integrins as key targets in wound healing, fibrosis and tumor stroma

The following section describes the cell type specific expression of integrins (summarized in Fig. 2) as well as their functional role in wound healing, tumor stroma, metastasis and kidney, liver and lung fibrosis (Table 2).

3.1. Wound healing

Wound healing is a common repair process after an injury to an organ. We describe the repair of cutaneous wounds in this section. Wound healing is based on the collective efforts of soluble mediators, blood cells, extracellular matrix and parenchymal cells [51]. This process consists of three timely overlapping stages namely, inflammation, tissue formation, and tissue remodeling [51]. During the innate inflammation, immune cells including neutrophils and granulocytes in the early phase and then macrophages, lymphocytes and mast cells are recruited into the wound. These immune cells release cytokines and chemokines that recruit epithelial cells and fibroblasts to the wound edge [6]. Thereafter, epithelial cells start to stretch into the wound bed, followed by proliferating keratinocytes, which seed more cells into the wound site during re-epithelialization [6]. Parallel to re-epithelialization, granulation tissue formation is initiated which is closely associated with wound angiogenesis [6]. During this process, epithelial cells are recruited into the wound by cytokines and create the granulation tissue together with myofibroblasts and pericytes [6]. Myofibroblasts facilitate wound contraction and closure which is followed by tissue remodeling, during which myofibroblasts degrade, remodel and reorganize the ECM [6]. During the complex wound healing process, cells bind to ECM molecules within the wound via their integrin receptors resulting in integrin's functional activation or induced expression. Integrin receptors with a functional role in wound healing are listed in Table 2.

Integrin β1 is an important integrin because it is a subunit in many different heterodimers. Integrin β1 deficiency in mouse fibroblasts, correlates with reduced expression of α-smooth muscle actin (α-SMA), CCN2/CTGF and collagen I, and is accompanied by a reduced ability to activate latent TGFβ, thereby inhibiting differentiation of fibroblasts into myofibroblasts, resulting in delayed wound closure and reduced formation of granulation tissue [52]. Integrin αvβ3 has shown to be inhibitory to the fibroblast infiltration into the wound clot. Mice deficient of integrin β3 showed accelerated re-epithelialization, which is associated with enhanced TGFβ signaling and dermal fibroblast infiltration into wounds [39]. Integrin α1β1 is expressed on cells of the basement membrane including vascular, visceral, endothelial, smooth muscle cells and pericytes, and on cells of the connective tissue including fibroblasts, chondrocytes, mesenchymal stem cells and circulating white blood cells [53]. The collagens that bind integrin α1β1 include collagen I, III, IV, XIII, XVI [53]. Modulating the collagen-binding integrin activity could therefore also be an interesting approach to improve the healing of chronic wounds.

Integrin α2β1 is expressed on keratinocytes, epithelial cells and endothelial cells which are in contact with the basement membrane and on fibroblasts, T-cells, myeloid cells, megakaryocytes and platelets which are in contact with matrices rich in collagen I [54]. Integrin α2β1 specifically binds to collagen I, III, IV, V, XI, XVI and XXIII [54]. Next to collagens, integrin α2β1 also binds to the proteoglycans, biglycan, lumican, fibromodulin and decorin, and a proteolytic fragment derived from perlecan called endorepellin [54]. It has been shown that binding of fibroblasts to collagen within 3D-matrices activates p38α MAP kinase pathway and results in increased integrin α2β1-dependent collagenase-3 (MMP13) synthesis [54,55].

Mice deficient in α1 and α2 demonstrated minor changes in their ability to remodel granulation tissue ECM, this is likely because other collagen-binding integrins compensate for most of their function, including MMP expression and collagen fibrillogenesis [6]. Integrin α3β1 is expressed on basal cells of epidermis and other epithelia [56]. Conditional knockout of integrin α3β1 in the epidermis of mice (keratinocytes) resulted in impaired angiogenesis within wounds, which is correlated with reduced expression of the angiogenesis promoting mitogen-regulated protein 3 (MRP3) [57]. These finding suggest a role of α3β1 in promoting wound angiogenesis through MRP3-mediated crosstalk from epidermal to endothelial cells [57].

Table 2
Integrins and their function in wound healing, tumor stroma, metastasis, kidney, liver and lung fibrosis.

Integrin	Expressional modification	Function	Cell/tissue type/disease	Ref.
Wound healing				
β3	Genetic knockdown	Accelerated re-epithelialization, enhanced TGFβ signaling, dermal fibroblast infiltration	Fibroblasts, epithelial cells	[39]
β1	Fibroblast specific knockout	Delayed cutaneous wound closure and reduced granulation tissue formation, including reduced production of new ECM and reduced αSMA expression	Fibroblasts	[52]
α3β1	Epidermal knockout	Impaired angiogenesis	Keratinocytes, endothelial cells	[57]
α5β1	Overexpression	Interaction of overexpressed integrin α5β1 leads to T Cell driven keratinocyte proliferation	Keratinocytes	[59]
α5β1	None	Granulation tissue fibroblasts have a reduced ability to bind fibronectin via α5β1, increasing their migration ability	Fibroblasts	[60]
α9	None	Regulates migration and adhesion of dermal fibroblasts during granulation tissue formation in excisional wounds.	Dermal fibroblasts	[63]
αMβ2	Genetic knockdown	Delayed wound re-epithelialization	Neutrophils, monocytes	[66]
αvβ6	Overexpression	Spontaneous wound development with progressive fibrosis	Epithelial cells	[123]
αvβ6	Genetic knockdown	Delayed wound healing	Epithelial cells	[124]
αvβ5	None	Expressed in deep human and porcine wound during early re-epithelialization	Epidermis	[125]
αvβ5	None	Induced in keratinocytes during late mucosal and dermal wound healing	Keratinocytes	[126]
α2β1	Antibody blocking	Induces MMP-1 expression and collagen matrix denaturation in wounds	Keratinocytes	[127]
α5β1	Overexpression	Affects fibronectin integration and restricts keratinocyte migration	Keratinocytes	[128,129]
α11β1	Genetic knockdown	Reduced granulation tissue formation and impaired wound contraction	Fibroblasts	[65]
α3β1	None	Determines the migrational directionality of keratinocytes	Keratinocytes	[130]
β1	β1 deficient keratinocytes	Impaired migration and wound healing. β1 deficiency is accompanied by α6β4 downregulation	Keratinocytes	[131]
α3β1	Genetic knockdown	Inhibits directional migration and re-epithelialization	Keratinocytes	[132]
Kidney fibrosis				
β6	Genetic knockdown	Prevents tubulointerstitial fibrosis	Kidney	[67]
α3	Genetic knockdown	Reduced neovascularization; delayed kidney fibrosis and neovascularization	Kidney	[70,71,133]
α2β1	Genetic knockdown	Knockdown delays the maturation of the glomerular basement membrane and kidney fibrosis in Alport mice	Kidney	[71]
α11β1	None	Crucial for the regulation of the myofibroblast phenotype	Myofibroblasts in UUO kidneys in mice and human fibrotic kidneys	[72]
β6	Genetic knockdown	Knockdown inhibits renal fibrosis in Alport mice	Kidney	[73]
αvβ1	None	blockade of αvβ1 prevents the activation of latent TGFβ1 through direct binding by fibroblasts	Fibroblasts in the kidney	[74]
α8	Genetic knockdown	De novo expression in interstitial fibroblasts and tubular endothelial cells in tubulointerstitium fibrosis. Knockdown did not inhibit tubulointerstitium fibrosis, but increased tubulointerstitium damage compared to wild type mice	Fibroblasts and endothelial cells in tubulointerstitium fibrosis	[75]
α3	None	Mediates kidney fibrosis via integrin-linked kinase through mediated loss of E-cadherin	Kidney fibrosis	[76]
Liver fibrosis				
β6	Genetic knockdown	Prevents acute biliary fibrosis	Liver	[67]
α3, α6	None	Expression of these integrins indicate a switch of hepatocytes into bile duct epithelial cells	Hepatocytes in cholestasis	[77]
β1, α1, α5, α6	None	Integrin expression positively correlates with the stage of fibrosis	Liver	[78]
β1	None	Integrin expression level positively correlates with the stage of fibrosis.	Chronic hepatitis C & B, PBC, PSC	[79]
β1	None	Overexpressed on T lymphocytes	Alcoholic liver disease	[80]
αL, αM αX, α4	None	Expression levels on peripheral blood leukocytes positively correlated with liver failure	Leukocytes in liver cirrhosis	[82]
αLβ2, α4β1	None	Integrin expression correlates with infiltrating lymphocytes	Lymphocytes in PBC	[83]
αvβ6	None	Upregulated	Biliary atresia	[84]
β2	None	Induced expression of integrin β2 on neutrophils increases their migration and Kupffer cell release of chemotactic cytokines and growth factors	Chronic alcohol intoxication of the liver	[86]
αL	None	Indirectly promotes fibrosis	Lymphocytes in PBC	[87]
β6	Genetic knockdown	Knockdown inhibits neutrophil infiltration and plasma transaminase activity as well as hepatic necrosis		[88]
β6	Genetic knockdown	Knockdown inhibits neutrophil infiltration and plasma transaminase activity as well as hepatic necrosis	Acute cholestatic hepatitis	[89]
β1	None	Responsible for the recruitment of CD16(+) monocytes into the liver	Chronic liver inflammation and fibrogenesis	[90]
α5β1	None	Increases collagen production via integrin α5β1/ECM induced changes in the cytoskeletal organization and activation of Src kinases and ERK/JNK	Hepatic stellate cells in liver fibrosis	[91]
αv	Genetic knockdown	Protected mice from CCL4-induced liver fibrosis and was also protective in pulmonary and renal fibrosis	Myofibroblasts	[93]

Table 2 (*continued*)

Integrin	Expressional modification	Function	Cell/tissue type/disease	Ref.
α11β1	Genetic knockdown	Major regulator in the activation of HSCs into myofibroblasts	Myofibroblasts/liver fibrosis in mice	[72]
Lung Fibrosis				
αvβ6	Genetic knockdown	Regulates pulmonary fibrosis and inflammation by activating TGFβ	Epithelial cells of lung sclerosis and pulmonary fibrosis	[31]
αvβ8	Genetic knockdown	Increased pro-fibrotic differentiation of lung fibroblasts by regulating TGFβ activation. Increases the expression of collagen and pro-fibrotic genes.	COPD fibroblasts	[97–99]
αvβ5	None	Mediates TGFβ induced fibrosis.	Fibroblasts of pulmonary fibrosis	[100]
α3β1	Genetic knockdown	Knockdown correlates with reduced accumulation of myofibroblasts, collagen and EMT-associated genes	Pulmonary fibrosis	[102,103]
α11β1	none	Expression correlated concomitantly with the expression of various fibrotic parameters in the lungs of patients with IPF	Idiopathic pulmonary fibrosis	[72]
Tumor stroma				
α11β1	Genetic knockout	Expression positively correlates with prognosis. Induces IGF2 expression and tumorigenicity. Induces CXCL5 secretion by lung carcinoma cells.	Fibroblasts in lung adenocarcinoma	[49,108,110]
α11β1	None	Overexpressed in the tumor stroma. Expression positively correlates and co-localizes with the expression of αSMA	Head and neck squamous cell carcinoma	[105]
α5β1	None	Desmoplastic traits prognostic of neoplastic recurrence of integrin α5β1 are maintained by matrix regulated integrin αvβ5	Cancer-associated fibroblasts in pancreatic cancer	[106]
α11β1	None	Promotes invasion	Invasive breast cancer cells	[109]
α9β1	None	Osteopontin-rich matrix activates TAMs through ligation of integrin α9β1, stimulating the migration of endothelial and cancer cells via prostaglandin E2 production	Melanoma model	[111]
αvβ3	None	Periostin, secreted by glioblastoma stem cells, promote TAM recruitment to tumors via integrin αvβ3 signaling.	Glioblastoma xenografts	[112]
Metastasis				
α2β1	Genetic knockdown	Expression is associated with favorable prognosis and reduced tumor cell intravasation	Breast cancer, squamous cell carcinoma	[115,116]
α2β1	None	Accelerated levels increase experimental metastasis	metastasis in melanoma, gastric and colon cancer	[117–119]
αvβ5	None	Expressed in vascular structures and tumor stroma and associated with high hypoxia inducible factor 1α indices	Brain metastasis of lung cancer	[121]
αvβ3	None	Expressed on vascular structures and associated with low Ki-67 indices	Brain metastasis of lung cancer	[121]
β1, β3	None	Overexpressed and correlate with cancer progression and metastasis in the liver.	Liver metastasis of colorectal cancer	[122]

During wound healing, fibronectin (Fn) is activated and assembled into a fibrillary structure Fn matrix that is known to be promoted by integrin α5β1. Fibroblasts adhesion to the provisional matrix (composed of Fn and fibrin) via integrin α5β1 in the initial stage of wound healing is enhanced when dermatopontin (a dermal ECM protein) co-localizes with fibrin and fibronectin in the wound clots [58]. Additionally, the interaction of α5β1 with fibronectin has shown to contribute to T-Cell lymphokine-driven keratinocyte proliferation next to facilitating matrix adhesion and motility [59]. It has been speculated that in fibroblasts, integrin α5β1 plays an important role *in vivo* during invasion of connective tissue cells into the wound clot and their migration in the fibrin-fibronectin-containing 3D wound environment [6]. Fibroblasts in the granulation tissue have a reduced ability to bind fibronectin via integrin α5β1 which might allow them to migrate in the early fibronectin-rich granulation tissue matrix [60]. Blocking of integrin α5 with antibodies *in vitro* in human oral mucosa and dermal fibroblasts were capable of blocking TGFβ-induced expression of α-SMA [61]. This finding implies that novel therapeutic approaches targeting integrin α5 could present a strategy to inhibit α-SMA positive myofibroblasts which are closely associated with scar formation and various other pathological disorders.

In literature, increased integrin α9β1 expression is shown to induce retarded wound re-epithelialization, as shown in α9β1-deficient mice [6]. Furthermore, integrin α9β1 controls proliferation of keratinocytes and dermal fibroblast by interacting with elastic microfibril interface-located protein 1 (EMILIN1) [62]. Additionally, blocking of integrin α9β1 on integrin-positive dermal fibroblasts with a specific antibody inhibited the formation of granulation tissue in cutaneous wound healing, showing that integrin α9β1 is involved in the formation of granulation tissue by regulating the migration and adhesion of dermal fibroblasts in excisional wounds [63].

Integrin α11β1 expression has also been shown to be expressed restrictively to a subset of fibroblasts and mesenchymal stem cells *in vivo* [54] and is the main collagen receptor on dermal fibroblasts, contributing to collagen remodeling in a TGFβ-dependent manner [64]. Zweers *et al.* were the first to demonstrate the role for integrin α11β1 in dermal wound healing, in which α11β1 is strongly induced in mice after inflicting excisional wounds [65]. Dermal wounds in integrin α11β1 deficient mice showed a reduction in granulation tissue formation and wound strength 7 days after excisional wound infliction, which is attributed to a defect in myofibroblasts differentiation, indicating α11β1-dependent collagen remodeling within granulation tissue [64]. Next to its role in collagen remodeling, integrin α11β1, similar to integrin α5β1, is involved in myofibroblast differentiation and granulation tissue formation, as a response to injury, and thereby contributes to scar formation. This implies integrin α11β1 as a potential therapeutic target and it would be of very high interest to investigate the effects of therapeutic blocking of this integrin in the context of myofibroblast differentiation during scar formation and pathological fibrosis in general.

In addition to fibroblasts and epithelial cells, integrins play a key role in immune cells such as neutrophils, monocytes and certain lymphocytes. Integrin αMβ2 is a leukocyte receptor which is involved in immune cell recruitment and the activation of inflammatory responses during wound healing [66]. Integrin αMβ2 is capable of engaging various ligands including ECM proteins, counter receptors as intracellular adhesion molecule 1 (ICAM-1) and coagulation and complement products. Ligand binding by integrin αMβ2 affects leukocyte adhesion and activation [66]. Knockout of integrin αMβ2 in mice has been shown to be correlated with a delay in wound re-epithelialization and granulation

tissue formation but did not affect monocyte migration into the wound [66].

3.2. Fibrosis

In general, fibrosis is a response to organ injury and progressive fibrosis can lead to major organ failure and ultimately lethality [3,67]. Organ fibrosis is characterized by a complex interplay between inflammatory, epithelial, myofibroblast, and excessive ECM production and deposition [3,67]. The highly dynamic pericellular ECM of the fibrotic tissue exerts profound influences on the behavior of the surrounding cells [3]. Many of the main cell-cell and cell-matrix interactions that regulate fibrosis are mediated by integrins [3]. The expression and function of integrins in kidney, liver and lung fibrosis are described in the following section and is listed in Table 2.

3.2.1. Kidney fibrosis

Integrins α1β1 and α2β1, the major collagen binding receptors, and laminin receptors α3β1 and α6β1 are highly expressed in the healthy kidney [68]. Integrin α1β1 binds to collagen IV, and deletion or inhibition of α1β1 exacerbates glomerulosclerosis suggesting that activation of α1β1 integrin might be beneficial for renal injury [69]. In contrast to Integrin α1β1, integrin α2β1 is a positive regulator of collagen synthesis and reactive oxygen species production. Studies propose that Integrin α2β1 induces glomerular fibrosis and absence of α2β1 delays kidney fibrosis and glomerular injury in experimental models for kidney disease [70,71]. Knockdown of the discoidin domain receptor 1 (DDR1) and integrin α2β1 delays the maturation of the glomerular basement membrane, which causes renal fibrosis in the Col4A3 deficient−/− mice, a mouse model of Alport syndrome [71]. Additionally, in Col4A3 deficient−/− Alport mice with impaired glomerular basement membrane, maturation loss of integrin α2β1 delays kidney fibrosis [71]. An additional collagen binding integrin, integrin subunit α11 is specifically localized on myofibroblasts in UUO kidneys of mice and human fibrotic kidneys was found to be crucial for the regulation of the myofibroblast phenotype [72]. Moreover, its expression was significantly induced at an interstitial fibrosis and tubular atrophy score of 3, when compared to score 0–2 [72]. In Alport mice with a conditional knockdown of integrin β6, renal fibrosis was inhibited [73]. Furthermore, knockdown of integrin β6 partly or completely protects mice from tubulointerstitial fibrosis induced by kidney obstruction [67].

The expression of integrin αvβ1, αvβ3 and αvβ5 was also identified on renal fibroblasts and blockade of αvβ1 prevented the activation of latent TGFβ1 through direct binding by fibroblasts [74].

While in the healthy kidney, integrin α8 is only expressed in mesangial cells and vascular smooth muscle cells, de-novo expression of integrin α8 was found on interstitial fibroblasts and tubular epithelial cells undergoing de-differentiation in tubulointerstitial fibrosis induced by the unilateral ureteral obstruction model [75]. Furthermore, studies in mice with knockdown of integrin α8 revealed that underexpression of α8 did not inhibit tubulointerstitial fibrosis, but increased tubulointerstitium damage compared to wild type mice [75]. Therefore, targeting integrin α8 threapeutically does not seem to be a useful antifibrotic strategy.

Moreover, integrin α3 has shown to induce kidney damage attributed to loss of E-cadherin induced by integrin α3-dependent Src/p-β-catenin-Y654/p-Smad2-mediated up-regulation of integrin-linked kinase [76].

In summary, integrin α1β1, α2β1, αvβ3, α3 and α8 have been identified to play a role in kidney fibrosis. Inhibiting integrin α2β1 and αvβ3 in kidney fibrosis seems to have high potential as a therapy, while induction of integrin α1β1 and integrin α3, via e.g. an RNAi approach, also seems to have therapeutic potential.

3.2.2. Liver fibrosis

In healthy liver, different integrins are expressed on various cell types controlling specific functions to maintain homeostasis. Vascular endothelium expresses many integrins such as α1, 2, 3, 4, 5 and 6; bile duct epithelium express integrin α2, 3, 5 and 6; stroma of the connective tissue integrin α1 and 2; hepatocytes integrin α1 and 5; sinusoidal lining cells integrin α1, 2, and 5; and mononuclear cells integrin α4 [77]. During liver pathogenesis, the altered expression levels and de novo expression of integrins have been reported in preclinical and clinical studies. Nejjari *et al.* performed a clinical study including 94 patients with chronic hepatitis C, in which the expression of integrin β1, α1, α5 and α6 was significantly upregulated and showed correlation with the stage of fibrosis [78]. In a different study, integrin β6 was shown to correlate with the stage of fibrosis in the livers of patients with end-stage liver disease, including chronic hepatitis B & C, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) [79]. Mice with integrin β6 knockdown or blocking antibody to αvβ6 significantly decreased acute biliary fibrosis after bile duct ligation [67]. In patients with alcoholic liver disease, integrin β1 was significantly overexpressed on T lymphocytes (and/or hepatocytes) when compared with healthy patients [80,81]. In liver cirrhosis, integrin αL, αM, αX and α4 expression levels on peripheral blood leukocytes was positively correlated with liver failure [82]. During cholestasis, the hepatocytes show de novo expression of integrin α3 and α6, indicating that they undergo a phenotypic switch from hepatocytes to bile duct epithelium [77]. In PBC, integrin αLβ2 (lymphocyte function associated antigen 1 (LFA-1)) and α4β1 (very late antigen 1 (VLA-4)) were found to be expressed on infiltrating lymphocytes, while control livers showed no or weak expression of these integrins [83].

In addition to these clinical studies, integrin αvβ6 was found to be upregulated in rotavirus-induced biliary atresia, resulting in liver fibrosis [84]. Rats with a chronic alcohol intoxication showed an induced expression of integrin β2 on neutrophils, which increased their migration (most probably mediated by osteopontin via α4β1 and α9β1 integrins [85]) and Kupffer cells mediated release of chemotactic cytokines and growth factors [86]. Moreover, in PBC, integrin αL (CD11a) was found to be expressed on T lymphocytes but is absent in chronic hepatitis C or healthy patients, indicating a role of CD4+ integrin αL expressing lymphocytes in Th-1 predominance and might thereby indirectly promote fibrosis [87]. Mice with an integrin β2 knockout showed reduction in hepatic necrosis, decreased number of intrahepatic neutrophils and plasma transaminase activity during acute and chronic cholestatic liver injury [88,89]. In chronic liver inflammation and fibrogenesis, integrin β1, activated by vascular adhesion protein-1 and CX_3 chemokine receptor 1 has been proposed to be responsible for the recruitment of CD16(+) monocytes into the liver [90]. Activation of HSCs increased the expression of integrin α5β1, and α5β1/ECM crosstalk induced collagen production via changes in the cytoskeletal organization, and activation of Src kinases and ERK/JNK signaling molecule families [91]. Expression of integrin α8β1 is induced in activated HSCs following bile duct ligation or CCl_4 induced hepatic injury in rats [92]. Genetic knockdown (Pdgfrb-Cre) of integrin αv, protected mice from CCL4-induced liver fibrosis and was also protective in pulmonary and renal fibrosis [93]. Very recently, Bansal *et al.* [72], have identified integrin subunit α11 as a major regulator in the activation of HSCs into myofibroblasts. Knockdown of integrin subunit α11 in HSCs inhibited their differentiation and functionality in response to TGF-β [72]. Integrin subunit α11 expression was found to be regulated by the hedgehog pathway and inhibition of hedgehog led to inhibition of HSC induced fibrosis in mice. This work highlights integrin subunit α11 as a highly promising therapeutic target in liver fibrosis [72].

3.2.3. Lung fibrosis

Integrin αvβ6, a receptor for the ECM proteins fibronectin [94] and tenascin C [36] is minimally expressed in alveolar epithelial tissues but is highly induced upon lung injury, resulting in lung fibrosis [95].

Integrin αvβ6 has been demonstrated to be overexpressed in the epithelium of lung sclerosis and pulmonary fibrosis [67]. Genetic knockdown of integrin β6 in mice was introduced to attenuate bleomycin-induced pulmonary fibrosis and radiation induced pulmonary fibrosis [31,67]. Recently, integrin α6β1, upregulated in fibrotic lung myofibroblasts, was identified as a mechanosensor for matrix stiffness, [96]. Upon sensing matrix stiffening during pulmonary fibrosis α6β1 mediates MMP-2 dependent pericellular proteolysis of basement membrane collagen IV, thereby regulating invasion of myofibroblasts [96]. The expression of integrin αvβ8 is highly expressed in the airways of chronic obstructive pulmonary disease (COPD) patients and correlates with the severity of the obstruction [98,99]. Additionally, COPD fibroblasts show increased pro-fibrogenic differentiation upon αvβ8 mediated TGFβ1 activation [97,98]. Knockdown of αvβ8 in murine lung fibroblasts reduced TGFβ-activation in these cells [99]. Deletion of αvβ8 in lung fibroblasts resulted in inhibition of airway fibrosis in IL-1β and ovalbumin-induced mouse models [99]. Additionally, the authors demonstrated that IL-1β increased αvβ8-dependent TGFβ activation, collagen expression and pro-inflammatory gene expression in human COPD compared to normal human lung fibroblasts [99]. In patients with idiopathic pulmonary fibrosis, integrin αvβ5 causes TGFβ-mediated fibrosis and co-localizes with PAR1 (Protease-activated receptors) and the myofibroblast marker αSMA [100]. This process is inhibited by the blockade of integrin αvβ5 in mice [100]. Kim *et al.* showed that in idiopathic pulmonary fibrosis (IPF), alveolar epithelial cells undergo extracellular matrix triggered EMT, thereby turning into differentiating fibroblasts [101]. In an IPF mouse model with a lung specific deletion of integrin α3β1 reduced accumulation of myofibroblasts, collagen and genes associated with EMT were observed [102,103]. Integrin subunit α11 was in an additional study found to be significantly induced in the fibrotic lungs from patients with IPF were it co-localizes with α-SMA-positive myofibroblasts [72]. In addition, the expression of integrin subunit α11 correlated concomitantly with the expression of various fibrotic parameters in the lungs of patients with IPF [72].

3.3. Tumor stroma

The tumor stroma consists of non-cancerous cells including cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), pericytes, endothelial cells, and infiltrating immune cells [104]. More recently, stromal cells have been identified as drivers of tumorigenesis, promoting tumor growth, angiogenesis, invasion and metastasis [104]. Integrins that were found to be expressed in these cell types and their functional roles in the stroma are discussed in the following section and listed in Table 2.

Integrin α11β1 and α5β1 have been reported to be the main integrins expressed on fibroblasts within the tumor stroma [105,106]. Integrin α11β1 was found to be induced in a mechano-sensitive manner and contributes to TGFβ-dependent myofibroblasts differentiation *in vitro* [107]. A role for integrin α11β1 in tumorigenesis was first observed in lung adenocarcinoma in which α11β1 was identified as a tumor biomarker [108]. Specifically, integrin α11β was found to be overexpressed in the tumor stromal tissue of lung adenocarcinoma, where it induces IGF2 expression and tumorigenicity [49]. Furthermore, Integrin α11β1 is overexpressed in the tumor stroma of head and neck squamous cell carcinoma and its expression positively correlates and co-localizes with the expression of αSMA, a myofibroblast marker with prognostic value in head and neck squamous cell carcinoma [105]. Additionally, the gene encoding for integrin α11β1 (ITGA11), next to six other genes, was found to promote invasion, in a spheroid based model for the invasion of breast cancer cells [109]. Moreover, integrin α11β1 plays a role in the paracrine signaling between fibroblasts and cancer cells within tumor stroma. A study using 3D-heterospheroids composed of mouse embryonic fibroblasts (MEFs) and A549 lung carcinoma cells showed that CXCL5 expression in tumor cells was inversely related to integrin α11β1 in MEFs, indicating that integrin α11β1 increases the autocrine secretion of CXCL5 by lung carcinoma cells [110]. Franco-Barraza *et al.* have very recently introduced that desmoplastic traits, prognostic of neoplastic recurrence, dependent on integrin α5β1, expressed on myofibroblasts in pancreatic cancer, are maintained by matrix-regulated integrin αvβ5 [106]. In this work, the author's identified a CAF phenotype, with high expression of active integrin α5β1. Finally they propose a novel prognostic tool, in which they use stromal localization and levels of active Smad 2/3 and integrin α5β1 to distinguish patient-protective from patient-dentrimental desmoplasia, to foretell pancreatic cancer recurrence.

In addition to fibroblasts, integrins on macrophages also play a key role in tumor stroma. A recent study has implicated integrins in regulating the ability of TAMs to promote tumor progression. For example, in a melanoma model, an osteopontin-rich matrix activates TAMs through ligation of integrin α9β1, stimulating the migration of endothelial and cancer cells via prostaglandin E2 production [111]. Similarly, the ECM protein periostin, secreted by glioblastoma stem cells, promotes TAM recruitment to tumors via activation of αvβ3 [112].

These studies indicate that integrin α11β1, α5β1, α9β1 and αvβ3 play a crucial role in the tumor stroma by controlling the phenotype and behavior of key stromal cells. The integrins α11β1, α9β1 and αvβ3 show potential as therapeutic targets. In the context of drug delivery integrin α11β1 presents as a target with high potential, since the expression of this integrin is restricted to tumor stroma or other fibrotic disease but is generally not expressed in other tissues of the adult body. The design of novel integrin targeting ligands is therefore a highly interesting approach for drug delivery to CAFs.

3.4. Metastasis

Metastasis, which is defined as the spreading of cells from the primary tumor site to other organs is responsible for more than 90% of cancer-related lethality [113]. Integrins, are regulators of cell attachment to the ECM as well as cell migration and therefore have a crucial part in the regulation of metastasis [114].

Integrin α2 is widely expressed which makes it difficult to determine its function during tumorigenesis. High expression of integrin α2 in breast and prostate cancer correlates with a favorable prognosis [115]. Additionally, MMTV-neu mice lacking integrin α2 expression had increased tumor cell intravasation indicating that integrin α2 has metastasis suppressing properties [115]. Additionally, integrin α2β1 expression causes a decrease in lymph node metastasis in human papilloma virus-induced squamous cell carcinoma in mice [116]. In contradiction, elevated levels of integrin α2β1 accelerated experimental metastasis in melanoma, gastric and colon cancer [117–119]. Moreover, integrin α2β1 rich xenograft tumors, in mice have shown to promote metastasis to the bone [120].

The role of integrin α2 in tumorigenesis and metastasis is not yet clarified and appears to be dependent on expression levels and the tumor type [54]. Zeltz and Gullberg [54] hypothesized that high expression of integrin α2 in well-differentiated tumors might prevent metastasis, while tumors at other stages with low integrin α2 expression might support dedifferentiation and metastasis by directing metastasizing cells to collagen rich tissues, such as bone. In summary, integrin α2β1 could be further exploited as a biomarker. Since studies in integrin α2 knockout mice show no significant side effects integrin α2β1 additionally presents a potential therapeutic target to attenuate metastasis, but this strategy seems only applicable for not-well-differentiated tumors with low collagen expression.

In a clinical study including lung cancer patients with brain metastases (BM), high expression of integrin αvβ5 on vascular structures and tumor stroma (in BM) was found to be associated with high hypoxia inducible factor 1α (HIF1α) indices, while αvβ3 was expressed on vascular structures and tumor cells (in BM) and was correlated with low Ki-67 indices [121]. Although it would be of high interest to see what effects new therapeutic agents against αvβ5 might have on the

Table 3
Therapeutics for integrin inhibition in development.

Integrin target	Compound name	Stage (year)	Cellular target	Disease target	Reference
αv-Family integrins					
αvβ3	Vitaxin	Phase I (2000)	Endothelial cells	Breast, lung and colon cancer	[135]
αvβ3	Etaracizumab	Phase I (2005, 2008)	Endothelial cells	Several solid tumors	[136,137]
αvβ3	Etaracizumab	Phase II (2010)	Endothelial cells	Metastatic melanoma	[138]
αv	CTNO 95	Phase I (2007)	Endothelial and tumor cells	Several solid tumors	[139]
αv	CTNO 95	Phase II (2013)	Endothelial and tumor cells	Castration-resistant prostate cancer	[140]
αv	CTNO 95	Phase I (2015)	Endothelial and tumor cells	Several solid tumors	[141]
αvβ3, αvβ5	Cilengitide	Phase II (2006)	Endothelial and tumor cells	Prostate cancer	[142]
αvβ3, αvβ5, αvβ1	Cilengitide	Phase I (2007) Phase II (2008) Phase III (2014)	Endothelial and tumor cells	Malignant glioma, glioblastoma	[143,144,180]
αvβ1	C8	Pre-clinical	Cancer-associated fibroblasts	Liver fibrosis, lung fibrosis, kidney fibrosis	[74,146]
αvβ1	c8	Pre-clinical	Activated fibroblasts	Bleomycin-induced pulmonary fibrosis, carbon tetrachloride-induced liver fibrosis	[146]
αv	CWHM 12	Pre-clinical		CCL4-induced liver fibrosis, bleomycin–induced lung fibrosis, cerulein-induced pancreatic fibrosis	[93,162]
αvβ6	Anti-αvβ6-mAb	Pre-clinical	Acinar cells, pancreatic stellate cells	Lung fibrosis, biliary fibrosis, liver fibrosis, renal fibrosis, kidney fibrosis	[73,148–151]
αvβ5	P1F6	Pre-clinical	Kidney fibroblasts, oral fibroblasts, dermal fibroblasts	/	[155]
αvβ3	LM609	Pre-clinical	Oral fibroblasts, dermal fibroblasts	/	[155]
αvβ6	STX-100	Phase II (2017)	/	Pulmonary fibrosis	[152]
αvβ3	Anti-αvβ3-mAb	Pre-clinical	Endothelial cells	Human wound tissue	[156]
αvβ6	EMD527040	Pre-clinical	Bile duct epithelial cells, Mdr2 (Abcb4)(−/−) mice with spontaneous biliary fibrosis	Liver fibrosis	[79,157]
αvβ3, αvβ6	ACDCRGDCFC-$(KLAKLAK)_2$	Pre-clinical	Endothelial cells	/	[158]
αvβ3	Echistatin, αv RNAi, antiβ3	Pre-clinical	Hepatic stellate cells	Liver fibrosis	[159]
αvβ3, αvβ5	Cilengitide	Pre-clinical	Hepatic stellate cells	Experimental liver fibrosis	[160]
αv	Anti-integrin alpha V	Pre-clinical	Hepatic stellate cells	Liver fibrosis	[161]
α5-Familiy integrins					
α5β1	Volociximab	Phase II (discontinued, 2006–2011)	Endothelial cells	Ovarian cancer, peritoneal cancer, pancreatic cancer, renal cancer	[164–168]
α5β1	Volociximab	Phase I (discontinued, 2008, 2013)	Endothelial cells	Advanced solid malignancies, non-small-cell lung cancer	[163,169]
α5β1	RGD	Pre-clinical	Hepatic stellate cells	Liver cirrhosis	[171]
α5β1	PF-4605412 (Mab)	Phase I (discontinued, 2013)	Endothelial cells	Solid malignancies	[170]
αvβ3, α5β1	ATN-161	Pre-clinical	Endothelial cells	Breast cancer	[172]
αvβ3, α5β1	ATN-161	Phase I (2006)	Endothelial cells	Solid tumors	[173]
α2-Family integrins					
α2β1	E7820	Phase I (2011)	Endothelial cells	Advanced solid tumors	[174]
β1	OS2966	Pre-clinical	Endothelial cells	Glioblastoma	[176]
α1β1	Obtustatin	Pre-clinical	Endothelial cells	Lung cancer	[177]
αL, αM and β2-Family integrins					
αLβ2	Anti–LFA-1 antibody	Pre-clinical	Leukocytes	Liver fibrosis	[178]
αM	Anti-CD11b antibody	Pre-clinical	Monocytes	Liver infection	[179]
β2	1F12	Pre-clinical	Neutrophils in the liver	Experimental alcoholic hepatitis	[86]

expression of HIF1α in BM, it could be argued that αv integrins are not a feasible therapeutic target, because blocking of these integrins could be associated with severe side effects, due to their wide expression in the human body. The expression of αv integrins is still of pathological and clinical relevance in lung cancer patients with brain metastasis and it might be interesting to explore them as biomarkers.

In colorectal cancer, CD98, integrin β1, β3 and FAK was overexpressed and correlated with cancer progression and metastasis in the liver [122]. Direct contact between the tumor stroma and tumor cells is required for these markers to be over-expressed in metastasis of the liver [122].

In summary, integrins seem to play a crucial role in the regulation of metastasis within certain tumors. Especially integrin α2β1 has, dependent on tumor stage and type, potential as a therapeutic target in metastasis, while integrin αvβ3, αvβ5, β1 and β3 should be validated for their use as biomarkers. Unfortunately, none of the integrins discussed show a very specific expression in pathological tissues, but are widely expressed, which makes these integrins poor targets for drug targeting.

4. Therapies based on integrins inhibition

Various different integrins have been identified to play a role in fibrosis and their knockdown or blocking has been shown to dampen disease progression. An example of a clinically approved integrin inhibitor is the integrin α4β7 inhibitor vedolizumab, selectively inhibiting lymphocyte trafficking, which is applied as a treatment in Crohn's disease [134]. Therefore integrin-specific inhibitors have a huge potential as anti-fibrotic therapeutics. An overview of therapies (pre-clinical and clinical) based on integrin inhibition are described in the following section and are summarized in Table 3.

5. αv-Family integrins

The majority of integrin targeting drugs tested in clinical trials inhibit αv integrins. In the context of this review, it is important to realize that αv integrins are generally expressed in the blood vessels and various other endothelial tissues and in the case of cancer, these drugs may target tumor cells, next to angiogenic vessels of the tumor microenvironment. Although integrins are abundantly present on tumor cells, in this review we focus on tumor stromal cells and we therefore only mention integrin αv inhibiting therapies, which clearly demonstrated effects on these cells.

An antibody, so-called, vitaxin against αvβ3, which was later evolved into etaracizumab was tested in phase I and II clinical trials with low toxicity. Therapeutic efficacy but no immunogenicity was observed after treatment with etaracizumab in metastatic melanoma and other solid tumors. However, further development of etaracizumab was terminated based on the results of a randomized clinical trial in which its efficacy was compared to standard chemotherapy showing no meaningful improvement [135–138].

Another antibody against αvβ3 and αvβ5, CTNO 95, has been tested in phase I clinical trials in advanced solid tumors showing anti-tumor activity and no toxicity [139]. Hereupon, CTNO 95 together with docetaxel and prednisolone was evaluated in a multicenter phase II clinical trial for safety and efficacy in patients with castration-resistant prostate cancer in which CTNO 95 caused a shorter progression free survival without showing additional toxicity compared to placebo treatment [140]. Later CNTO 95 was tested in combination with bevacizumab in a phase I biomarker study in patients with advanced solid tumors, could be administered safely and resulted in changes of the plasma levels of soluble endoglin, soluble E-cadherin, and soluble E-selectin as well as PlGF and VEGF-D, all proteins which interact with the ECM [141]. The selective αvβ3 and αvβ5 blocker cilengitide, based on the cyclic RGD peptide was successfully tested in phase I and II clinical trials for lung cancer, prostate cancer and glioblastoma but failed to enhance the survival benefit in patients when cilengitide was given in addition to the standard of care therapy [142–145]. Using a small molecule inhibitor for integrin αvβ1, Reed *et al.* [146] found that αvβ1 directly binds to the latency-associated peptide of TGFβ1, thereby mediating TGFβ activation. Administration of this small molecule inhibitor showed therapeutic efficacy by attenuating bleomycin-induced pulmonary fibrosis and carbon tetrachloride-induced liver fibrosis but has not been evaluated in clinical trials [146].

Antibody mediated blocking of the TGFβ activating integrin αvβ6 has shown therapeutic activity in a wide range of pre-clinical fibrosis models. These models include models for lung fibrosis [147,148], liver fibrosis [149,150] and renal fibrosis [73,151]. A humanized monoclonal antibody, STX-100 (BG00011), against αvβ6 is currently being tested in phase 2 clinical trials in patients with idiopathic pulmonary fibrosis [152]. Genetic knockdown of β6 and functional antibody blocking of αvβ6 in renal fibrosis attenuates the accumulation of activated fibroblasts and interstitial collagen matrix deposition [73]. Treatment of scleroderma fibroblasts with antibodies against integrin αvβ3 and αvβ5 reduced the expression of procollagen type I [33,34,40,153,154]. Antibody mediated blocking of the integrins αvβ3 and αvβ5 inhibits myofibroblast differentiation in oral and dermal fibroblasts *in vitro*, while the inhibition of differentiation of kidney fibroblasts was only achieved with antibody blocking of αvβ3 [155]. A monoclonal antibody against αvβ3 blocked fibroblast growth factor (FGF), tumor necrosis factor-alpha and human melanoma fragments induced angiogenesis in human wound granulation tissue [156]. A small molecule inhibitor of αvβ6 (EMD527040) inhibited bile duct proliferation and peribiliary collagen deposition, decreased the expression of pro-fibrotic and induced fibrolytic genes [157]. In Mdr2 (Abcb4)(−/−) mice with spontaneous biliary liver fibrosis, a single dose of a selective αvβ6 inhibitor significantly induced profibrolytic MMP-8 & -9, and showed downregulation of the fibrosis markers procollagen α1, TGFβ2 and MMP-2 [79].

The integrins αvβ3 and αvβ6 targeting peptide ACDCRGDCFC has been conjugated to the pro-apoptotic antimicrobial synthetic peptide $(KLAKLAK)_2$ and has shown selective toxicity to angiogenic endothelial cells, by disrupting their mitochondrial membranes, and showed anti-cancer activity in mice [158].

Hepatic stellate cells, precursors of liver myofibroblasts, are one of the major sources of ECM production in liver fibrosis, which makes them a target for anti-fibrotic therapeutics. Zhou *et al.* found that inhibition of integrin αvβ3 with neutralizing antibodies, echistatin or small inhibitory RNA to silence the αv subunit expression, decreased proliferation of hepatic stellate cells [159]. More recently, the αvβ3 inhibitor Cilengitide was used to treat liver fibrosis in rat, induced by bile duct ligation (BDL) or thioacetamide (TAA) injections, and resulted in a significant decrease of liver fibrosis and collagen deposition, but increased experimental liver fibrosis (~30%) [160]. By blocking both ICAM-1 and integrin αv on hepatic stellate cells, phagocytosis of fibrosis promoting lymphocytes, a process mediated through members of the Rho family (Cdc42 or Rac-1) and leading to the activation of hepatic stellate cells was completely prevented [161].

Genetic knockdown and blocking of integrin αvβ6 with antibodies prevented radiation–induced pulmonary fibrosis [148] and hepatic fibrosis induced by biliary obstruction in mice [149]. The small molecule inhibitor C8 binding to αvβ1 in picomolar concentrations, significantly inhibited liver and lung fibrosis in mice, reducing collagen deposition by approximately 50% [146]. In a renal unilateral obstruction model, administration of C8 inhibited collagen deposition and effectively attenuated renal failure [74]. Another small molecule inhibitor blocking αv, CWHM 12, attenuated CCl4-induced liver fibrosis, bleomycin–induced lung fibrosis as well as cerulein-induced pancreatic fibrosis in mice [93,162]. Although, most therapeutic approaches inhibiting integrins are directed against αv there are only a handful of compounds which have made it to clinical trials and those have failed to show improved therapeutic efficacy, which might be related to off-target binding of these inhibitor due to the wide expression of integrin subunit αv.

6. α5-Family integrins

An additional target for anti-cancer therapy is integrin α5β1, known to be expressed on CAFs, angiogenic vessels and tumor cells. A humanized monoclonal antibody, specifically binding to α5β1, volociximab, showed absence of severe toxicities in patients with solid tumors and resulted in one minor response and disease stabilization in another case in a phase I clinical trial [163]. A phase II study with volociximab was performed in patients with relapsed malignant melanoma showing insufficient effects to proceed to stage 2 of the study [164]. The subsequent phase II study evaluating volociximab in refractory metastatic clear cell renal cancer resulted in stable disease in 87% of the patients [165]. This study is continued in a follow-up in which higher dose levels are being evaluated in patients [165].

In metastatic pancreatic cancer, volociximab was studied in combination with gemcitabine in which 5% had confirmed partial response and 50% of the patients showed a stable disease [166]. In a phase II study in platinum resistant advanced epithelial ovarian or primary peritoneal cancer, volociximab showed insufficient clinical activity [167]. Another study in recurrent ovarian or primary peritoneal cancer, volociximab was used in combination with pegylated liposomal doxorubicin, showing no statistically significant difference when compared to pegylated doxorubicin alone [168]. In a phase I dose escalation study of volociximab in combination with carboplatin and paclitaxel in patients with advanced non-small cell lung carcinoma showed promising clinical efficacy, but the development of this therapy has not been developed further [169]. Another integrin α5β1 monoclonal antibody developed by Pfizer, PF- 4605412 has also been evaluated in phase I

clinical trials and has been discontinued due to the acute infusion-related reactions [170].

An integrin α5β1 binding RGD peptide inhibited the progression of CCl4-induced liver fibrosis and collagen deposition in the liver [171]. Additionally, RGD inhibited the expression of collagen 1 and tissue inhibitor of MMP-1 and increased MMP-1 expression of human hepatic stellate cell derived cells *in vitro* [171].

Another α5β1 targeting peptide derived from the synergy region of fibronectin, binding to α5β1 and αvβ3, ATN-161 (Ac-PHSCN-NH2) caused a dose-dependent decrease in tumor volume and inhibited metastasis in a metastatic mouse breast cancer model [172]. In a phase I clinical trial in patients with solid tumors, ATN-161 caused no dose limiting toxicities [173]. Unfortunately, no objective responses to ATN-161 treatment were found, but prolonged stable disease was observed in patients with renal cancer [173].

7. α2-Family integrins

A small molecule inhibitor of integrin α2β1 (E7820) was investigated in phase I clinical trials for the treatment of metastatic colon cancer and is currently tested in phase II clinical trials in combination with cetuximab [174,175].

8. β1-Family integrins

Since integrin β1 is a partner receptor for many α receptor units, it is present ubiquitously. In bevacizumab-resistant glioblastomas (BRG) integrin β1 mediates interactions between the tumor and its microenvironment [176]. These interactions include tumor cell binding to ECM-ligands like fibronectin, collagen IV and laminin, and VEGF-dependent as well as independent vascularization [176]. Treatment of BRG mouse xenografts with the integrin β1 specific antibody, OS2966, allowed a reduction in the dose of bevacizumab and delivery of OS2966 over a period of 28 days showed increased apoptosis of tumor cells and a decrease in tumor cell invasiveness and mesenchymal morphology of tumor cells [176].

A 41 amino acid peptide, purified from the venom of the *Vipera lebetina obtusa* viper is an effective inhibitor of integrin α1β1 and inhibited angiogenesis and tumor growth *in vivo* in the chicken chorioallantoic membrane assay and the Lewis lung syngeneic mouse model [177].

9. αL, αM and β2-Family integrins

αL and αM-family integrins antibody mediated blocking of integrin αLβ2 in mice that underwent bile duct ligation decreased the activity of alanine aminotransferase and aspartate aminotransferase levels in serum. Additionally the adhesion of leukocytes in bile duct ligation induced post-sinusoidal venules was reduced [178]. Integrin αM and CD44 blockage with antibody reduced the localization of monocytes to hepatic foci [179]. Additionally, treatment of rats with the neutropenic monoclonal antibody 1F123 against integrin β2, capable of forming heterodimer with integrin αM, αL, αX and αD, attenuated alcohol initiated hepatic injury [86].

10. Drug targeting strategies based on integrin ligands

Extensive work has been done in the design of new ligands for integrin receptor targeting that can be utilized for integrin facilitated drug delivery or imaging. A large portion of these ligands are targeting

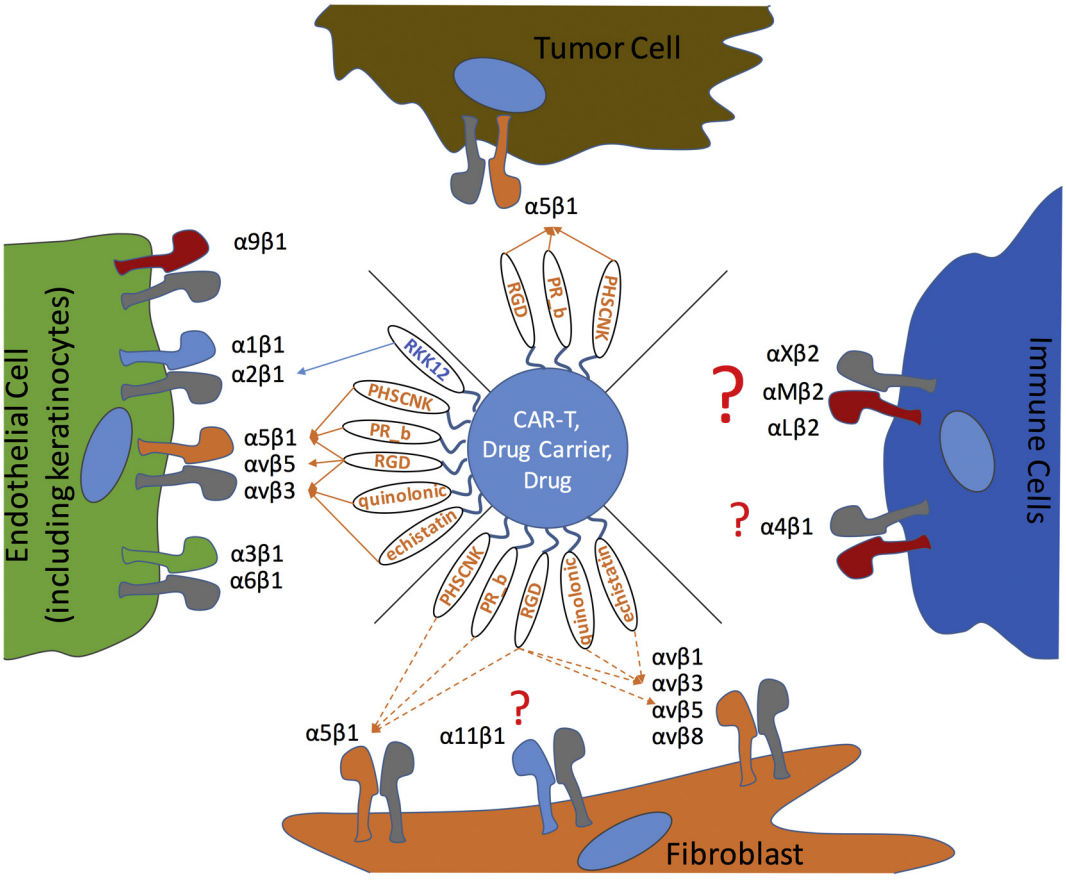

Fig. 3. Existing integrin drug targeting ligands, applied for the modification of drug molecules, drug carriers and CAR-T cells (CAR-T), in the context of wound healing, fibrosis or tumor stroma and their respective integrin targets. Dashed lines show potential integrin targets for existing ligands that have not yet been used for targeting the respective cell line. In addition to already targeted integrins, integrins that have not yet been targeted but play a role in the pathology of wound healing, fibrosis or tumor stroma are presented.

RGDs and have been extensively reviewed in a recent article by Arosio *et al.* [181]. Therefore, RGD based targeting approaches have been excluded from this review, unless it has been shown that they have facilitated specific targeting to components related to fibrosis, wound healing or the tumor stroma. The followig section describes integrin targeting ligands, applied for the modification of drug molecules, drug carriers and CAR-T cells (CAR-T), in the context of wound healing, fibrosis and tumor stroma. (See Fig. 3.)

Ruoslahti *et al.* have developed two peptides binding to the αv binding motifs Arg-Gly-Asp (RGD) and Asn-Gly-Arg (NGR), and coupled these to the anti-cancer drug doxorubicin. Targeting the tumor vasculature of human breast cancer xenografts in mice, resulted in enhanced efficacy of doxorubicin [182]. Targeting doxorubicin to endothelial cells by linking a bicyclic CDCRGDCFC (RGD-4C) peptide selectively binding to integrin αvβ3 and αvβ5 and a D-Ala-Phe-Lys tripeptide selectively binding to tumor-associated protease plasmin to the drug, resulted in plasmin-dependent cytotoxicity of endothelial cells [183]. The cyclic RGD compound containing the conformational constrained homoSer-Pro dipeptide unit with a fluorescent probe for αvβ3-imaging has shown to possess the ability to bind endothelial cells *in vitro* [184]. A new αvβ3-specific tumor vessel binding cyclic peptide containing the iso-DGR motif was conjugated to albumin and coupled to tumor necrosis factor-α (TNF-α) carrying gold nanoparticles [185]. These nanodrugs showed inhibited tumor growth in WEHI fibrosarcoma bearing mice [185].

The integrin α5β1 antagonistic peptide ATN-161 in combination with the chemotherapeutic agent 5-fluorouracil significantly reduced liver metastasis, tumor microvessels as well as increased tumor cell apoptosis and decreased tumor cell proliferation, resulting in an increased overall survival in mice [186]. Later, ATN-161 was investigated in phase II trials in cancer [187]. The PHSCNK peptide targeting α5β1 was applied to modify Dox-loaded liposomes to enable targeting of the tumor vasculature and showed enhanced cytotoxicity to endothelial and breast cancer cells, which was attributed to integrin mediated endocytosis [188]. Mardilovich *et al.* have designed a integrin α5β1 specific peptide PR_b, mimicking the cell binding site of native fibronectin [189]. Later this peptide has been applied to target siRNA and polymerosomes, lipoplexes, polyplexes and stealth liposomes to integrin α5β1 [190–192]. Peptidomimetic integrin ligands selectively binding to either α5β1 or αvβ3 in fibroblasts functionalized with 1-((1,3-dicarboxy) propyl)-4,7-(carboxymethyl)-1,4,7-triazacyclononane (NODAGA) successfully targeted α5β1 or αvβ3 expressing tumors in mice. Additionally, both peptidomimetics inhibited tumor growth in syngeneic subcutaneous WEHI-164 fibrosarcomas in mice by inhibiting α5β1 or αvβ3, respectively [193,194].

Modification of cisplatin with platinum (IV) complexes conjugated to the αvβ3/αvβ5-specific peptide motifs RGD, (CRGDC)c, (RGDfK)c or NGR to target tumor endothelial cells, showed anti-proliferative effects on human endothelial cells *in vitro* [195]. Pan *et al.*, have modified PEGylated perfluorooctylbromide (PFOB) nanoparticles (NPs) carrying the anti-angiogenic fumagillin with a quinolonic αvβ3-integrin ligand conjugated to the PEG chain of these NPs. This drug delivery system decreased angiogenesis in a Matrigel plug assay for angiogenesis in mice [196].

Fu *et al.*, have modified chimeric antigen receptor (CAR) T cell with echistatin, having a high binding affinity to integrin αvβ3. The echistatin expressing T cells were capable to efficiently lyse HUVECS, resulting in the extensive bleeding of the tumor tissue *in vivo* without damaging blood vessels in normal tissues and facilitated specific penetration of liposomes into the tumor site [197].

11. Conclusions and future directions

Despite a lot of work being done to gain insight in the biological role of integrin subtypes in wound healing, fibrosis and tumor stroma, there is still a need to better understand their significance and implications. Most studies have been carried out by the means of integrin subunit knockout in mice or using integrin-specific inhibitory antibodies. A few studies have revealed integrins with a role in fibrosis, which resulted in some potential anti-fibrotic therapeutics. However, most of them failed in early or late clinical trials. It is worth mentioning that integrin αv and β1 are the most studied integrin receptors because they are the partner receptors of many heterodimeric receptors. RGD and its derivative peptide sequences binding to αv and β1 units are the most studied ligands against integrins with therapeutic potential. However, most of them are not specific to one but various integrin receptors.

Furthermore, it is very important to realize that integrin αv and β1 are widely expressed within the human body and are not specifically expressed. Some of the cells types which express integrin αv and β1 include e.g. endothelial cells and tumor cells. Therefore, molecules targeting αv or β1 integrins are prone to exert off target effects. This could also explain why inhibitors such as Cilengitide, which have made it to phase III clinical trials have finally been terminated. Especially in fibrosis related diseases, it could be an interesting approach to develop molecules targeting integrins with a more disease-specific expression which are not involved in angiogenesis but for example expressed on myofibroblasts or tumor associates macrophages, two of the main drivers of disease progression in fibrosis, tumor stroma and wound healing. Therefore, studies exploiting the expression of a specific integrin subunit and its cellular localization within pathological tissues and other healthy organs are crucial to determine novel integrin-based therapeutic targets. Moreover, the design of integrin subunit specific drugs will decrease the risk of off-target effects due to a high specificity of these molecules. An additional major aspects for the identification of integrin subunits as therapeutic targets is to have a clear understanding of integrin subunit – growth factor interactions.

Furthermore, with regard to drug targeting approaches, mainly targets of RGD-based targeting peptides binding to integrin αvβ3, αvβ5, αvβ6 and α5β1 have been applied. Also in this context targeting of non-disease-specific integrins and integrin subunits can lead to off target effects and could results in severe toxicities, depending on the payload of the delivery system, even if the targeting molecule itself does not exert toxic effects.

Another important point to consider with regard to RGD-based targeting approaches is a finding by Kunjachan *et al.* [198] which showed that passive targeting of 10 nm-size polymeric nanocarriers resulted in enhanced intratumoral nanoparticle accumulation and retention when compared with RGD-peptide modified polymeric nanoparticles. These observations might be different for targeting systems with a larger size but it should be taken into consideration that targeting approaches directed towards targets with a more specific expression within a certain disease might increase site-specific accumulation and retention and additionally reduce side effects.

In conclusion, studies which have revealed the biological function of various integrins within fibrosis related disease, although not completely understood, imply various novel therapeutic and drug targeting targets. One of the major challenges remaining is to use the knowledge obtained on integrin biology to develop highly integrin subunit specific targeting molecules, which can be applied as therapeutics by themselves or utilized as targeting ligands in disease-specific drug delivery systems.

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