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CORRECTION

The integrin–collagen connection – a glue for tissue repair?

Cédric Zeltz and Donald Gullberg

There was an error published in *J. Cell Sci.* **129**, 653–664.

In Fig. 2A, the fibroblasts were incorrectly labelled. The correct annotation should have been $\alpha11^{-/-}$ fibroblast (left) and $\alpha11^{+/+}$ fibroblast (right). The correct Fig. 2 is shown below.

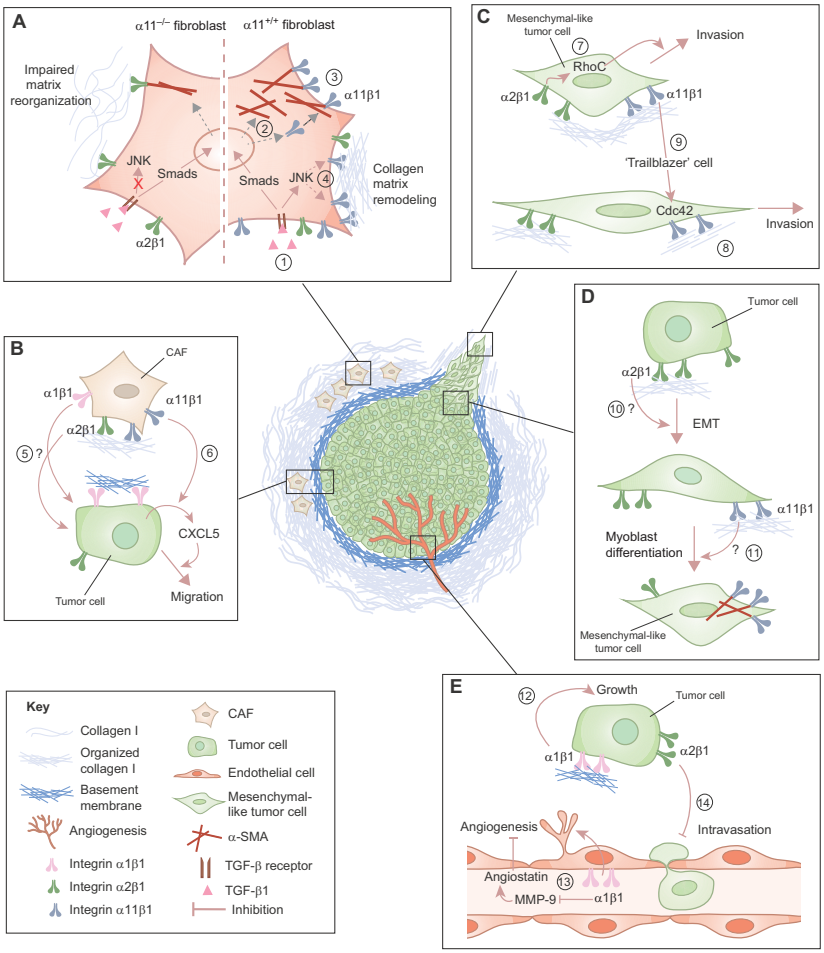

Fig. 2. Roles of collagen-binding integrins in cancer. (A) Integrin α11β1 in collagen reorganization. α11β1 promotes collagen remodeling, whereas α11 deficiency leads to impaired matrix reorganization (Schultz et al., 2015). (1) Binding of TGF-β to its receptor, induces α-SMA expression and (2) upregulates α11 expression through Smad signaling. (3) α11 is necessary to stabilize α-SMA protein expression. (4) α11β1 integrin reorganizes collagen matrices through TGF-β-induced JNK signaling. (B) Collagen-binding integrins in tumor–stroma interaction. (5) α1β1 and α2β1 are expressed on cancer-associated fibroblasts (CAF), but how this affects tumor cells is so-far unclear. However, (6) α11β1 on fibroblasts can modulate autocrine secretion of CXCL5 in lung adenocarcinoma cells to promote tumor cell migration (Lu et al., 2014). (C) Collagen-binding integrins in tumor invasion. (7) α2β1 promotes prostate cancer invasion through RhoC activation (Hall et al., 2008). α11β1 is one of the seven genes identified as a signature for the 'trailblazer' cell phenotype (Westcott et al., 2015). (8) Trailblazer cells lead collective invasion and generate pathways within collagen matrices that also allow opportunist follower cells to invade. (9) α11β1 and Cdc42 are both involved in the formation of the long cell protrusions needed for invasion. (D) Collagen-binding integrins in epithelial-to-mesenchymal transition (EMT). (10) Collagen-binding integrins do not appear to have a major role in EMT. (11) Because α11β1 is expressed on mesenchymal-like tumor cells, it might have a role in myofibroblast differentiation of mesenchymal-like tumor cells. (E) Collagen-binding integrins in angiogenesis. (12) α1β1 is expressed on tumor cells, and promotes tumor growth and metastasis (Chen et al., 2005). (13) α1β1 is also expressed on endothelial cells, where it promotes angiogenesis (Pozzi et al., 2000), and downregulates levels of active MMP-9, which suppresses the production of the angiogenesis inhibitor angiostatin. By contrast, (14) the presence of α2β1 on tumor cells inhibits tumor cell intravasation during the metastatic process (Ramirez et al., 2011).

We apologise to the readers for any confusion that this error might have caused.

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COMMENTARY

The integrin–collagen connection – a glue for tissue repair?

Cédric Zeltz and Donald Gullberg*

ABSTRACT

The α1β1, α2β1, α10β1 and α11β1 integrins constitute a subset of the integrin family with affinity for GFOGER-like sequences in collagens. Integrins α1β1 and α2β1 were originally identified on a subset of activated T-cells, and have since been found to be expressed on a number of cell types including platelets (α2β1), vascular cells (α1β1, α2β1), epithelial cells (α1β1, α2β1) and fibroblasts (α1β1, α2β1). Integrin α10β1 shows a distribution that is restricted to mesenchymal stem cells and chondrocytes, whereas integrin α11β1 appears restricted to mesenchymal stem cells and subsets of fibroblasts. The bulk of the current literature suggests that collagen-binding integrins only have a limited role in adult connective tissue homeostasis, partly due to a limited availability of cell-binding sites in the mature fibrillar collagen matrices. However, some recent data suggest that, instead, they are more crucial for dynamic connective tissue remodeling events – such as wound healing – where they might act specifically to remodel and restore the tissue architecture. This Commentary discusses the recent development in the field of collagen-binding integrins, their roles in physiological and pathological settings with special emphasis on wound healing, fibrosis and tumor–stroma interactions, and include a discussion of the most recently identified newcomers to this subfamily – integrins α10β1 and α11β1.

KEY WORDS: Collagen, Fibrosis, Integrins, Tumor, Wound repair

Introduction

Within the integrin family, the integrins that bind to RGD sequences have been extensively studied owing to their demonstrable importance for development, angiogenesis and thrombosis, and also on account of their roles in activating transforming growth factor beta (TGF-β) and fibrosis (Barczyk et al., 2010; Hynes, 2007, 2009; Munger and Sheppard, 2011). The RGD-binding integrins have, thus, served in many instances as prototypes in order to understand the details of integrin activation and function. By comparison, the collagen-binding integrins α1β1, α2β1, α10β1 and α11β1 have been living in the shadow of these prototypes, partly because of their relatively limited roles in embryonic development and also because of the relatively mild phenotypes observed in mice that lack individual collagen-binding integrins (Popova et al., 2007b; Zeltz et al., 2014). In addition, there are also technical limitations, for instance the complexity of authentic synthetic triple helical peptides for the collagen-binding integrins as compared with the far simpler linear RGD-containing peptides.

The picture of collagen-binding integrins playing a relatively minor role in normal physiology contrasts with the severe phenotypes that have been documented when the ligands of these integrins – members of the collagen family – are defective (Zeltz et al., 2014). Recent data, however, have highlighted the contribution of the collagen-binding integrins to fibroblast function in wounds (Schulz et al., 2015), in fibrotic tissue (Talior-Volodarsky et al., 2015) and tumor models (Lu et al., 2014; Navab et al., 2015). These findings, which establish important roles for collagen-binding integrins in relation to fibroblasts, are timely and fit well into the recent awareness that wound healing, fibrosis and tumor–stroma interactions share key mechanisms at the molecular level (Rybinski et al., 2014). This Commentary focuses on the collagen-binding integrins and their biological roles, summarizing some basic facts and recent findings that might change our view of collagen-binding integrins.

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Indirect binding to collagens: the nectin and COLINBRI concepts

Before the identification of the integrin family, cells were thought to be anchored to collagens indirectly through tissue-specific nectins [from *nectere* (lat.): to bind, join together]. One such nectin is osteonectin, now known as secreted protein acidic and rich in cysteine (SPARC), which is present in bone and binds Ca^{2+} and collagen I (Termine et al., 1981). Another example is chondronectin, which was thought to mediate cell attachment to collagen II in cartilage (Hewitt et al., 1982). When integrins were identified and found to be a large family of receptors with versatile roles in cell adhesion, this concept went out of fashion (Barczyk et al., 2010). The identification of collagen-binding integrins appeared to be the last nail in the coffin for the nectin concept, and clearly demonstrated that cells can bind directly to monomeric and fibrillar forms of certain collagens without the need for an indirect linkage (Camper et al., 1998; Gullberg et al., 1995; Kramer and Marks, 1989; Santoro, 1986). On the basis of our current understanding, however, it is possible that cells *in vivo*, in addition to direct collagen binding, also indirectly bind to fibrillar collagens. We have introduced the term COLINBRIs for proteins that bridge the interactions of cells with native fibrillar collagens, as discussed more thoroughly in a previous review (Zeltz et al., 2014).

Direct binding to collagens: the non-integrin collagen-binding receptors

In addition to the collagen-binding integrins α1β1, α2β1, α10β1 and α11β1 (Leitinger, 2011; Zeltz et al., 2014), the collagen-binding receptors include a number of other proteins with affinities for various types and forms of collagen, such as platelet glycoprotein VI (GPVI) (Clemetson et al., 1999; Kehrel et al., 1998; Zahid et al., 2012), discoidin domain receptor tyrosine kinases 1 and 2 (DDR1 and DDR2) (Leitinger, 2014; Vogel et al., 1997), leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1) (Meyaard, 2008, 2010), osteoclast-associated immunoglobulin-like receptor (OSCAR) (Barrow et al., 2011) and G-protein-coupled receptor 56 (GPR56, gene name *ADGRG1*) (Luo et al., 2012) (Fig. 1).

Whereas the direct and indirect binding to collagen through integrins serve as mechanolinks, the other collagen-binding receptors have more heterogeneous functions and, in general, tend to affect cellular signaling rather than serving as mechanolinks between fibrillar collagen matrices and the cytoskeleton.

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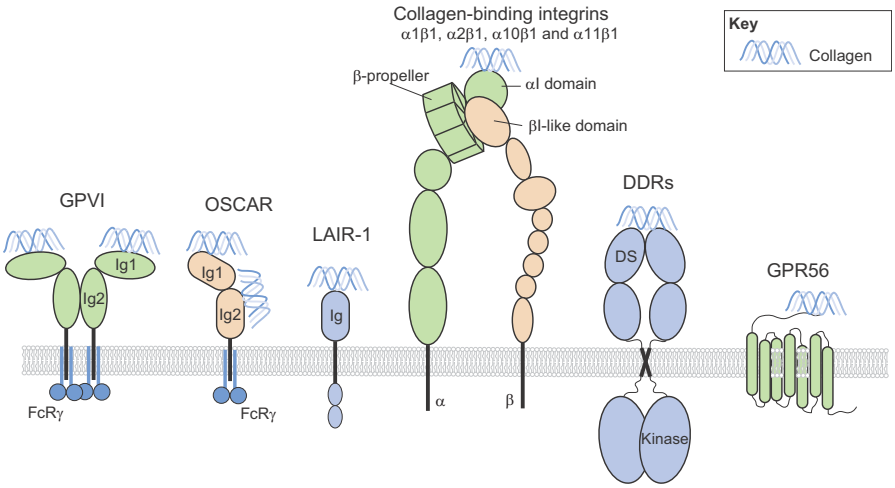

Fig. 1. Collagen receptors. Schematic of structures for the collagen receptors discussed in this Commentary. GPVI and OSCAR are composed of two immunoglobulin-like (Ig) ectodomains, and are associated with a dimeric Fc receptor γ chain at the cytoplasmic tail. Collagen interacts with the Ig1 domain and, in the case of OSCAR, with both the Ig1 and Ig2 domain. GPVI forms a dimer, whereas dimerization of OSCAR has not been observed. LAIR-1 interacts with collagen through its Ig ectodomain. Integrins comprise one α and one β subunit. Collagen-binding integrins display an αI domain on the α subunit, to which collagen binds. Discoidin domain receptor tyrosine kinases (DDRs) are homodimeric collagen receptors; collagen binds through the discoidin (DS) ectodomain. GPR56 is a G-protein-coupled receptor composed of seven transmembrane domains. Collagen interacts with the long extracellular N-terminal region of GPR56.

GPVI is an important collagen-binding immune receptor on platelets, with an activating role that is independent of integrin α2β1 (Marjoram et al., 2014; Zahid et al., 2012). Recent data suggest that it can also bind laminin isoforms and fibrin (Alshehri et al., 2015; Inoue et al., 2006). Significantly, its binding to human placenta laminin (a mixture of laminins-211, -411 and -511) is of lower affinity than that to collagen I and relies on α6β1 integrin-mediated activation of GPVI (Inoue et al., 2006; Wondimu et al., 2006).

LAIR-1 is present on immune cells (Meyaard, 2010) where it generates inhibition signals because binding to collagens inhibits LAIR-1 function. The collagen-like protein surfactant D (SFTPD) has recently been shown to be another ligand for this immune inhibitory receptor (Abbonante et al., 2013; Olde Nordkamp et al., 2014).

OSCAR is present on osteoclasts, where it co-stimulates osteoclastogenesis with receptor activator of NF-κB (RANK) (Barrow et al., 2011), and its absence on bone marrow macrophages leads to osteoclast differentiation defects. This receptor has also been shown to have a role in the maturation of human monocyte-derived dendritic cells (Schultz et al., 2015). The protein surfactant D has recently been shown to be an OSCAR ligand (Barrow et al., 2015).

DDRs are tyrosine kinases that are activated by collagens (Vogel et al., 1997); they have been found to be important in bone (Labrador et al., 2001) and mammary gland development (Vogel et al., 2001). DDRs have recently been shown to be able to activate collagen-binding integrins (Abbonante et al., 2013; Staudinger et al., 2013; Xu et al., 2012).

GPR56 is present on meningeal fibroblasts, oligodendrocytes, melanoma cells and cytotoxic NK and T lymphocytes (Chiang et al., 2011; Peng et al., 2011; Yang and Xu, 2012). Human GPR56 mutations cause a brain malformation called bilateral frontoparietal polymicrogyria (Chiang et al., 2011). Interestingly, the observed brain phenotype of GPR56-deficient mice appears to be phenocopied in the brains of collagen-III-deficient mice and is further enhanced by integrin α3β1 deficiency (Jeong et al., 2013; Luo et al., 2012). More recently, ablation of GPR56 has pointed to a cell-autonomous function in oligodendrocyte development (Giera et al., 2015). GPR56 also binds to other ligands, including tissue transglutaminase 2 (Yang et al., 2014).

Direct binding to collagens: the collagen-binding integrin receptors

The collagen-binding integrins are members of the β1 integrin (also known as CD29) subfamily. The collagen receptors α1β1 and α2β1 were first identified in the mid-1980s on subsets of activated T-cells (Hemler et al., 1985a,b) and, later, shown to be collagen receptors present on multiple cell types (Ignatius et al., 1990; Staatz et al., 1989). The last member of the integrin family, integrin α11β1, was cloned in 1999 (Velling et al., 1999), just after the characterization of α10 in 1998 (Camper et al., 1998). Thus, considerably less data have been accumulated for these two last additions to the integrin family. As collagen-binding integrins have been extensively reviewed in the past few years (Leitinger, 2011; Zeltz et al., 2014), we here emphasize their biological roles with a special focus on integrins α10 and α11.

Integrin α1β1

Integrin α1β1 (the α1 subunit is also known as very late antigen-1, VLA-1, CD49a; gene name *ITGA1*) is widely expressed both on cells that are in contact with basement membranes (e.g. vascular, visceral and smooth muscle cells, pericytes and endothelial cells) and on connective tissue cells, such as fibroblasts, chondrocytes and mesenchymal stem cells, as well as also on circulating white blood cells (Gardner, 2014; Gardner et al., 1996). In some cell types, such as hepatocytes, α1β1 constitutes the only collagen-binding integrin receptor present (Gullberg et al., 1990).

Ligands for α1β1 include collagens I, III, IV, IX, XIII, XVI and the collagen IV chain-derived peptide arresten (Gardner, 2014; Hamaia et al., 2012; Nykvist et al., 2000) but this integrin prefers the non-fibrillar collagen IV to collagen I (Eble et al., 1993). *In vitro* studies have, furthermore, suggested that α1β1 prefers the monomeric form of collagen I to the fibrillar forms that are present in mature connective tissues (Jokinen et al., 2004). It is possible that contacts with mature fibrillar collagen I matrices are enabled through binding to fibril associated collagens with interrupted triple helices (FACIT) collagens, such as collagen XVI (Eble et al., 2006). Various laminin isoforms also serve as good ligands for α1β1 (Barczyk et al., 2010).

It has been suggested that α1β1 activates the adaptor protein Shc independently of focal adhesion kinase (FAK) (Wary et al., 1996) but later data, including signaling data in 3D environments, did not include any role for Shc binding in α1β1-mediated ERK signaling. The binding of α1β1 to ligand results in reduced collagen synthesis and reduced synthesis of matrix metalloprotease (MMP) (Jablonski et al., 2014; Ronzière et al., 2005). The cytoplasmic tail of α1 is the shortest of all integrin tails and it is interesting to note that this integrin uses elaborate interactions with growth factor receptors to mediate some of its effects (Chen et al., 2007; Mattila et al., 2008, 2005) (discussed below).

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Despite the prominent expression of integrin α1 in multiple tissues, the phenotype of α1-deficient mice is relatively subtle (Gardner et al., 1996; Zemmyo et al., 2003). *In vitro* studies suggest that this integrin can negatively regulate collagen synthesis but, because it also regulates collagen-degrading MMPs, a fibrotic phenotype in the skin of $\alpha1^{-/-}$ mice is only manifested when these are crossed with mice that express collagen I with a mutated collagenase cleavage site (Gardner et al., 1999). Although α1-deficient mice are normal in appearance, careful studies of this knockout strain by using a variety of challenging protocols have suggested a modulatory function for α1β1 in a number of tissues, including the kidney, the immune and musculoskeletal system and, most recently, the liver (see below).

At the molecular level, a role for α1β1 in maintaining kidney homeostasis has been demonstrated (Cosgrove et al., 2008; Moeckel et al., 2006; Zent et al., 2006) and the absence of α1 has been found to exacerbate glomerulosclerosis after glomerular injury by a mechanism that involves increased production of reactive oxygen species (Chen et al., 2004) (Table 1). Integrin α1β1 reduces the production of reactive oxygen species by downregulating the activation state of the profibrotic epidermal growth factor (EGF) receptor. This is achieved by controlling the level and phosphorylation state of caveolin-1, a scaffolding protein involved in receptor signaling and localization (Borza et al., 2010; Chen et al., 2007, 2010). In a mouse model for Alport syndrome ($COL4A3^{-/-}$ mice), α1β1-mediated transmigration of monocytes on collagen XIII that is produced by vascular endothelial cells has been described (Dennis et al., 2010). It has recently been demonstrated that integrin α1β1 negatively regulates unilateral ureteral obstruction-mediated tubulointerstitial fibrosis through a mechanism that involves the T-cell protein tyrosine phosphatase (TCPTP)-mediated downregulation of tyrosine phosphorylation

Table 1. Summary of the roles of collagen-binding integrins in fibrosis, inflammation and cancer

Integrin	Knockout phenotype	Wound healing in knockout models	Fibrosis in knockout models	Inflammation in knockout models	Cancer in knockout models
α1β1	Hypocellular skin (Gardner et al., 1996; Pozzi et al., 1998). Age-related osteoarthritis (Parekh et al., 2014; Zemmyo et al., 2003).	Normal (Gardner et al., 1999).	Increased experimental kidney fibrosis (Chen et al., 2004).	Reduced size of atherosclerotic plaques of more fibrotic composition (Schapira et al., 2005). Reduced experimental arthritis, reduced contact hypersensitivity (de Fougerolles et al., 2000; Ianaro et al., 2000), reduced DSS colitis (Krieglstein et al., 2002).	Reduced experimental tumor angiogenesis in breast cancer (Pozzi et al., 2000). Reduced experimental tumorigenesis in lung cancer models (Chen et al., 2005; Macias-Perez et al., 2008).
α2β1	Transient mammary gland developmental defect (Chen et al., 2002; Holtkotter et al., 2002) Delayed age-induced osteoporosis (Stange et al., 2013). Mild thrombus stability defect (He et al., 2003; Kuijpers et al., 2007).	Increased neoangiogenesis (Grenache et al., 2007; Zweers et al., 2007).	Reduced experimental kidney fibrosis (Borza et al., 2012; Rubel et al., 2014).	Reduced experimental arthritis (Peters et al., 2012), reduced DSS colitis (Gillberg et al., 2013; Lundberg et al., 2006), reduced bone loss (El Azreq et al., 2015), reduced inflammatory response of mast cells (Edelson et al., 2004), increased vascularization and reduced insulin resistance in diabetes model (Kang et al., 2011).	Increased breast cancer metastasis in the MMTV-neu model (Ramirez et al., 2011).
α10β1	Mild cartilage phenotype in mice (Bengtsson et al., 2005); chondrodysplasia in dogs (Kyöstilä et al., 2013).	ND	ND	ND	ND
α11β1	Defective incisor tooth eruption, dwarfed mice (Popova et al., 2007a). Human patients can live into their eighties (Sulem et al., 2015).	Reduced granulation tissue, reduced wound strength (Schulz et al., 2015).	Reduced fibrosis in a diabetes-induced cardiac fibrosis model (C. A. McCulloch*, personal communication).	ND	Reduced experimental NSCLC growth and metastasis (Navab et al., 2015; Zhu et al., 2007).

ND, not determined. *, Christopher A. McCulloch, Matrix Dynamics Group, University of Toronto, Toronto, Ontario, Canada.

levels within the cytoplasmic tail of TβRII, a variant of the type II TGF-β receptor, and results in dampening of the Smad-dependent profibrotic signaling in collecting-duct-derived cells (Chen et al., 2014). This phosphatase-dependent mechanism builds on a principle that is similar to the one first observed in the elegant original work by Mattila and colleagues, who described an α1β1-dependent effect on EGF receptor signaling (Mattila et al., 2005). As mentioned above, integrin α1β1 is expressed in chondrocytes and osteogenic cells. Reduced callus size and reduced cartilage production have been observed in bone fracture healing experiments, and it has been suggested that these effects correlate with a proliferation defect within mesenchymal precursor cells that occurs in the absence of α1β1 (Ekholm et al., 2002). Independent experiments have later demonstrated that osteoarthritis is accelerated in the absence of α1 (Zemmyo et al., 2003). α1β1 was first detected on T-cells (as VLA-1), and experiments with integrin $\alpha1^{-/-}$ mice suggested that lack of α1 attenuates inflammatory bowel disease (Krieglstein et al., 2002) and contact hypersensitivity (Suzuki et al., 2007). Pharmacological progress in blocking integrin α1 on human immune cells to reduce inflammation has, nevertheless, been slow, although anti-VLA-1 antibody treatment has been suggested to be beneficial to treat inflammatory conditions, such as rheumatoid arthritis and psoriasis, that involve localized pathological memory T-cells, (Gardner, 2014). A role for α1β1 in liver has recently been discovered, almost 20 years after the original integrin $\alpha1^{-/-}$ mouse strain was created, and recent data show that severity of obesity-induced fatty liver disease is attenuated in integrin $\alpha1^{-/-}$ mice (Williams et al., 2015). Although α1β1 is the only collagen receptor on hepatocytes (Gullberg et al., 1990), it does not seem to be involved in liver fibrosis. Instead, αvβ1 appears to play a role in liver through mechanisms that involve activation of TGF-β; a hypothesis derived from experiments conditionally deleting integrins from liver myofibroblasts (differentiated from the pericyte-like stellate cells) (Henderson et al., 2013; Reed et al., 2015).

In a tumor context, ablation of integrin α1 has been reported to attenuate tumor growth in a breast cancer model owing to the MMP-9-dependent generation of angiostatin (Pozzi et al., 2000), resulting in reduced angiogenesis (Fig. 2). Furthermore, the absence of α1 has been found to ameliorate or reduce tumor growth and metastasis in a number of lung cancer models (Chen et al., 2005; Macias-Perez et al., 2008). Careful investigation of the role of α1 in the colon has revealed that it is expressed on both epithelial cells and submucosal myofibroblasts (Boudjadi et al., 2013, 2015). Interestingly, increased levels of α1 in tumors can be found in the majority of colon cancer patients (Boudjadi et al., 2013), and it has recently been demonstrated that α1 expression is mediated by the transcription factor Myc, raising the possibility that α1 integrin is important in mediating the effects of Myc in colon cancer and other tumors (Boudjadi et al., 2015). Only limited information exists with regard to the expression of α1 in the tumor stroma, except for the above-mentioned role in tumor angiogenesis (Pozzi et al., 2000) and the expression of cancer-associated fibroblasts (CAFs) in colon cancer (Boudjadi et al., 2013; Rodriguez et al., 2009).

Integrin α2β1

The α2β1 integrin (the α2 subunit is also known asVLA-2, CD49b; gene name *ITGA2*) is widely expressed both on cells in contact with basement membranes (keratinocytes, epithelial cells, endothelial cells) and on cells that contact interstitial collagen-I-rich matrices, such as fibroblasts, T-cells, myeloid cells and megakaryocytes and/or platelets. It is, in fact, the only collagen-binding integrin expressed on platelets (Madamanchi et al., 2014b). Ligands for α2β1 include collagens I, III, IV, V and XI, as well as collagens XVI and XXIII (Jokinen et al., 2004; Kapyla et al., 2004; Kern et al., 1993). In addition to its collagen ligands, it also binds proteoglycans, such as lumican (Zeltz et al., 2010) and decorin (Fiedler et al., 2008) at sites distinct from the collagen-binding site present in the integrin αI domain. A proteolytic fragment derived from perlecan (also known as HSPG2), called endorepellin, also binds α2β1 (Bix et al., 2004; Woodall et al., 2008). Although α2β1 is abundantly expressed on cells that are in contact with basement membranes, its affinity for collagen IV is lower than that observed for collagen I (Heino, 2000; Käpylä et al., 2000). The ligand-binding I-domain of α2 has been crystalized together with a triple-helical peptide containing the GFOGER sequence (Emsley et al., 2000). Unlike what is the case for fibronectin matrices where the cell-binding site is exposed when fibronectin is coated to a stiff surface, the cell-binding site appears to be available to cells without any need for conformational change of the collagen (Seong et al., 2013). It is interesting to note in this context that binding of α2β1 to GFOGER-like motifs of collagen I can occur without the need for inside-out signaling (Nissinen et al., 2012; Siljander et al., 2004) (Box 1). Analyses of signaling pathways that are activated in fibroblasts within 3D collagen matrices have demonstrated α2β1-dependent activation of p38α MAP kinase (MAPK14) signaling and stimulatory effects on collagen synthesis (Ivaska et al., 1999; Ravanti et al., 1999).

Integrin α2β1 is also widely and abundantly expressed on specific cell types such as keratinocytes, and is thought to be the main collagen receptor on several epithelia and platelet cells. Unchallenged integrin $\alpha2^{-/-}$ mice appear to be largely normal but display a mild and transient defect in mammary gland branching (Grenache et al., 2007; Zweers et al., 2007). Despite a large body of data from α2β1 antibody-blocking experiments in various platelet assays and the reduced platelet response to collagen I observed *in vitro*, only a limited hemostatic defect has been observed *in vivo* that is largely restricted to an accessory role in thrombus stabilization (He et al., 2003; Kuijpers et al., 2007). Interestingly, in recent studies the selective α2 deletion in megakaryocytes has been found to result in reduced megakaryocyte differentiation and reduced platelet volume (Habart et al., 2013). It, thus, appears that we are far from understanding the full repertoire of α2β1 functions on platelets; these might only emerge in the years to come, as new and refined cell-specific genetic tools become available. As in the case of α1 integrin, extensive studies of integrin $\alpha2^{-/-}$ mice in various challenge experiments or disease models have revealed a number of phenotypes (Table 1). In view of its high expression on keratinocytes and its identification on dermal fibroblasts, the finding that α2β1 was not involved in keratinocyte migration or dermal fibroblast wound closure *in vivo* was surprising (Parks, 2007), even though increased neoangiogenesis was observed during wound healing (Grenache et al., 2007; Zweers et al., 2007). In a more recent study, reduced pathological neovascularization in integrin $\alpha2^{-/-}$ mice was observed in a model for retinopathy (Madamanchi et al., 2014a). The absence of α2 is known to delay fibrosis and glomerular damage in experimental kidney disease models, including the Alport syndrome mouse model (Borza et al., 2012; Rubel et al., 2014). Moreover, another more recent study has demonstrated a role for α2β1 in inflammation during rheumatoid arthritis, with reduced disease severity in integrin $\alpha2^{-/-}$ mice (El Azreq et al., 2015). Somewhat surprisingly, this protective effect was not due to the absence of α2 on immune cells as reported in a previous study (Gillberg et al., 2013). The finding of reduced levels of α2β1 in synoviocytes in two mouse models of arthritis, which results in decreased ERK activation and MMP-3 production, was thought to have caused the reduction of

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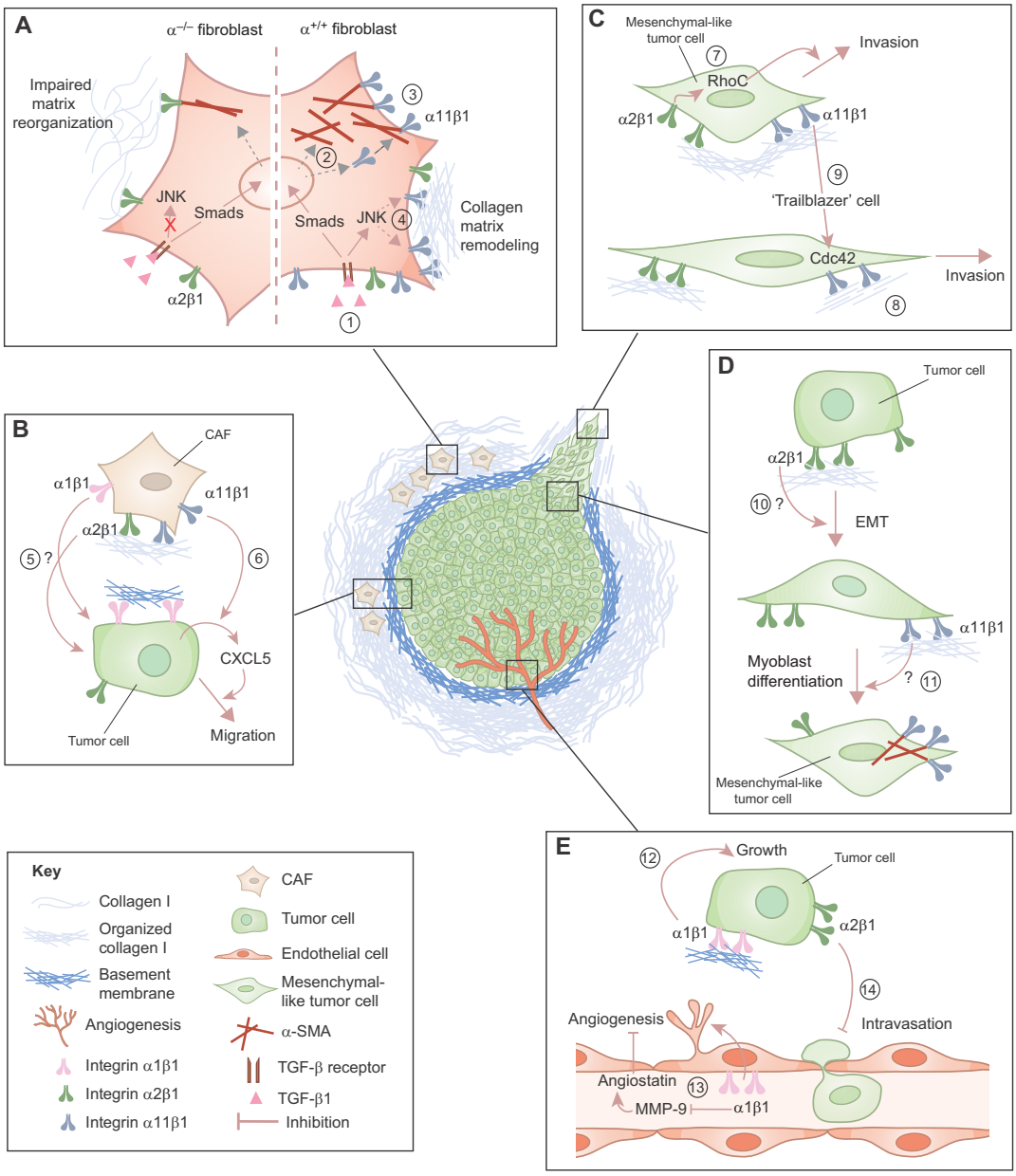

Fig. 2. Roles of collagen-binding integrins in cancer. (A) Integrin α11β1 in collagen reorganization. α11β1 promotes collagen remodeling, whereas α11 deficiency leads to impaired matrix reorganization (Schultz et al., 2015). (1) Binding of TGF-β to its receptor, induces α-SMA expression and (2) upregulates α11 expression through Smad signaling. (3) α11 is necessary to stabilize α-SMA protein expression. (4) α11β1 integrin reorganizes collagen matrices through TGF-β-induced JNK signaling. (B) Collagen-binding integrins in tumor–stroma interaction. (5) α1β1 and α2β1 are expressed on cancer-associated fibroblasts (CAF), but how this affects tumor cells is so-far unclear. However, (6) α11β1 on fibroblasts can modulate autocrine secretion of CXCL5 in lung adenocarcinoma cells to promote tumor cell migration (Lu et al., 2014). (C) Collagen-binding integrins in tumor invasion. (7) α2β1 promotes prostate cancer invasion through RhoC activation (Hall et al., 2008). α11β1 is one of the seven genes identified as a signature for the 'trailblazer' cell phenotype (Westcott et al., 2015). (8) Trailblazer cells lead collective invasion and generate pathways within collagen matrices that also allow opportunist follower cells to invade. (9) α11β1 and Cdc42 are both involved in the formation of the long cell protrusions needed for invasion. (D) Collagen-binding integrins in epithelial-to-mesenchymal transition (EMT). (10) Collagen-binding integrins do not appear to have a major role in EMT. (11) Because α11β1 is expressed on mesenchymal-like tumor cells, it might have a role in myofibroblast differentiation of mesenchymal-like tumor cells. (E) Collagen-binding integrins in angiogenesis. (12) α1β1 is expressed on tumor cells, and promotes tumor growth and metastasis (Chen et al., 2005). (13) α1β1 is also expressed on endothelial cells, where it promotes angiogenesis (Pozzi et al., 2000), and downregulates levels of active MMP-9, which suppresses the production of the angiogenesis inhibitor angiostatin. By contrast, (14) the presence of α2β1 on tumor cells inhibits tumor cell intravasation during the metastatic process (Ramirez et al., 2011).

pannus formation and cartilage erosion observed in $\alpha2^{-/-}$ mice (Peters et al., 2012). Studies of aging bone and cartilage further revealed defects in bone collagen dynamics and delayed age-induced osteoporosis in α2-deficient mice (Peters et al., 2012; Stange et al., 2013). Three decades after identification of the cell surface protein VLA-2 on T-cells (Hemler et al., 1985b), a recent study demonstrated that α2β1 cooperates with the interleukin 7 (IL-7) receptor on Th17 cells to mediate bone loss (El Azreq et al., 2015). Polymorphisms in the coding region of the α2 gene *ITGA2* have been observed to regulate α2 levels on human platelets (Kuncki and Nugent, 2010); and alleles encoding these variants were found in a separate study to be associated with an increased risk of thrombosis and myocardial

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Box 1. Modes of bi-directional integrin signaling

Outside-in signaling. Binding of integrin to ligand leading to a chemical signal being transmitted into the cell. This occurs by association of integrins with adapter proteins and soluble kinases and connect integrins, which themselves lack enzymatic activity, to signaling patwhays (Hynes, 2002).

Inside-out signaling. Conformation change in extracellular domain of integrin, regulating affinity for extracellular ligand. This occurs as a result of separation of cytoplasmic integrin tails which in turn takes place as a response to intracellular events leading to binding of the cytoskeletal proteins talin and kindlin to cytoplasmic tail of integrin β subunit (Harburger and Calderwood, 2009).

infarction (Santoso et al., 1999). The meaning of these findings is unclear but they indicate that the relative importance of integrin α2 in humans is different from that in mice. As α2β1 is widely expressed, it could be argued that it will never constitute a feasible therapeutic target, on account of potential side effects. However, studies of integrin $\alpha2^{-/-}$ mice suggest that α2 can be a target without significant side effects. Indeed, clinical trials in which antibodies against α2 were used to treat Crohn's disease and chronic autoimmune disorders are underway (http://newdrugapprovals.org/category/glenmark).

The role of α2 in tumorigenesis is difficult to dissect because of its wide expression. Comparing the experimental tumor data with human clinical data, high expression of α2 in both breast cancer and prostate cancer appears to correlate with a favorable prognosis (Ramirez et al., 2011); this is supported by MMTV-neu mice deficient in integrin α2, in which increased tumor cell intravasation was observed, suggesting that α2 serves as a metastasis suppressor (Ramirez et al., 2011) (Fig. 2). Intriguingly, α2 expression in xenograft models with prostate tumor cells can drive metastases to the bone, suggesting that the expression and functioning of α2 integrin on tumor cells is dynamic (Hall et al., 2006). High expression of α2 in a well-differentiated tumor may well prevent metastasis, whereas low expression at certain stages could promote dedifferentiation and metastasis. At other stages, however, high expression on metastasizing cells could direct these cells to collagen-rich tissues, such as bone (Hall et al., 2006). α2β1 is known to affect tumor growth and metastasis in a mouse model of squamous carcinoma (Tran et al., 2011), and high α2β1 expression has been reported to accelerate experimental metastasis in melanoma and gastric and colon cancer (Baronas-Lowell et al., 2004; Bartolomé et al., 2014; Matsuoka et al., 2000). Clinical trials are in progress for treating metastatic colon cancer by using a small-molecule inhibitor of α2β1, the sulphonamide E7820, (Mita et al., 2011).

In summary, the role of α2 in tumorigenesis and metastasis appears to vary depending on integrin α2 expression levels and type of tumor. Its role in the tumor stroma has not been explored in detail but α2β1 on fibroblasts could potentially act in order to reorganize the collagen matrix and alter its stiffness – as has been observed for lysyl oxidase (LOX) (Levental et al., 2009) and α11β1 (Navab et al., 2015) in experimental tumor models. To clarify the role of α2 in the tumor microenvironment it will be necessary to conditionally delete α2 on various cell populations within the tumor stroma.

Integrin α10β1

Integrin α10β1 (gene name *ITGA10*) appears to be primarily expressed *in vivo* on chondrocytes but also on some junctional fibroblasts, chondrogenic mesenchymal stem cells and cells lining the endosteum and periosteum (Camper et al., 2001; Gullberg and Lundgren-Åkerlund, 2002; Lundgren-Åkerlund and Aszòdi, 2014; Popov et al., 2011). Interestingly, the area around forming bone is rich in mesenchymal stem cells, and the treatment of these with fibroblast growth factor 2 (FGF2) concomitantly induces expression of integrin α10 and that of a chondrogenic phenotype (Varas et al., 2007). Furthermore, *ITGA10* mRNA expression is induced in bone-marrow-derived mesenchymal stem cells because these cells form the chondrogenic niches that are needed to establish a bone marrow microenvironment (Reinisch et al., 2015). Thus, several independent studies support a role for α10 integrin as a biomarker of chondrogenic stem cells (Lundgren-Åkerlund and Aszòdi, 2014).

Mice that are deficient in integrin α10 have a mild cartilage defect (Bengtsson et al., 2005) and, more recently, the analysis of inbred dog strains that present a truncating mutation in *ITGA10* has demonstrated full-blown canine chondrodysplasia (Kyöstilä et al., 2013) (Table 1). It is interesting to note that mutations in genes that encode components of the musculoskeletal system sometimes yield mild phenotypes in mice – which are short-lived and small, whereas, in larger animals, with a longer life-span, the same mutations may have more severe consequences.

Chondrosarcoma cells express α10β1, but its possible role in this form of tumor has not been assessed (Kapyla et al., 2004). Ligand-binding studies have suggested that α10β1 on chondrosarcoma cells can bind collagen IX as well as collagen II (Kapyla et al., 2004). Meanwhile, based on observations of fluctuating *ITGA10* RNA levels and following measurements of *ITGA10* promoter activity, it has been suggested that retinoblastoma protein (pRB) drives *ITGA10* expression and that the reduced levels of integrin α10 protein in cases of osteosarcoma depend on the presence of mutant pRB (Engel et al., 2013).

Perhaps more surprising is the finding that the largely cartilage-specific integrin α10 is expressed in melanoma cells. Furthermore, *in vitro* analyses have suggested a role for α10 in melanoma cell migration (Wenke et al., 2007). Since collagen II is not expressed in the dermis, this points to the existence of another collagen ligand for α10β1 in melanoma cells. One interesting candidate is collagen VI, which has recently been shown to affect hair growth in wounded skin (Chen et al., 2015). Single nucleotide polymorphism (SNP) analysis has revealed an ITGA10 SNP signature associated with favorable outcome for melanoma disease (Lenci et al., 2012).

Integrin α11β1

Expression of integrin α11β1 (gene name *ITGA11*) is primarily restricted *in vivo* to subsets of fibroblasts and to mesenchymal stem cells (MSCs). Transient expression of α11 in odontoblasts has also been observed (Popova et al., 2007a, 2004; Tiger et al., 2001; Velling et al., 1999); whereas, in bone marrow-derived non-haematopoetic MSCs, α11 was reported to be expressed on a small sub-fraction of cells able to undergo osteogenic differentiation (Kaltz et al., 2010). More notably, however, the sub-fraction of stem cells that undergo adipogenic differentiation do not express α11. In a separate study, it has been reported that MSCs depend on both α2 and α11 for osteogenic differentiation (Popov et al., 2011), and that knockdown of *ITGA2* and *ITGA11* in human mesenchymal stem cells reduces ERK and Akt signaling, and results in decreased cell proliferation and increased apoptosis (Popov et al., 2011). Mice deficient in α11 are dwarfed due to an incisor tooth eruption defect (Popova et al., 2007a), and an analysis of periodontal ligament fibroblasts isolated from their incisors demonstrated that reduced levels of MMP-13 and cathepsin K contributed to their reduced

capacity of collagen remodeling (Barczyk et al., 2013). The role of α11 in inflammatory conditions has not been tested directly but, recent findings that citrullination of the cell-adhesive GFOGER sequence within collagen selectively affects collagen binding mediated by α10β1 and, even more efficiently, α11β1 integrin (Sipilä et al., 2014), have spurred speculations that defective α11β1-mediated interaction of synovial cells with collagen might influence the pathological process involved in rheumatoid arthritis (Zeltz and Gullberg, 2014). This is an interesting possibility that remains to be tested.

The first indication that α11β1 is involved in dermal wound healing was the observation that α11 integrin is strongly induced in mice 7 days after inflicting excisional wounds (Zweers et al., 2007). The contribution of α11β1 to wound healing has recently been determined by using α11-deficient mice (Schulz et al., 2015) in which dermal wounds display reduced granulation tissue 7 days after excision due to a defect in myofibroblast differentiation (Table 1). This finding is in agreement with a previous study in which α11β1 was shown to contribute to TGF-β-induced myofibroblast differentiation *in vitro* (Carracedo et al., 2010). Integrin α11β1 is also important for the quality of the scar tissue because $\alpha11^{-/-}$ wounds display less tensile strength. This is indicative of an important role for α11β1 in collagen remodeling within granulation tissue. Despite the already described role of α2β1 in collagen reorganization *in vitro* (Zhang et al., 2006) and its expression on mouse dermal fibroblasts, α11β1 appears to be the main collagen receptor on dermal fibroblasts and contributes to early collagen remodeling in a TGF-β-dependent manner (Schulz et al., 2015) (Fig. 2). It is interesting, in this context, to note that, although TGF-β1 is known to regulate α11 integrin through Smad signaling (Lu et al., 2010), the involvement of non-canonical Jun N-terminal kinase (JNK)-dependent TGF-β signaling was shown to be crucial for α11β1-dependent collagen remodeling. Further studies are needed to determine the link between α11β1 and JNK activation. In this respect, TGF-β-activated kinase 1 (TAK1) is an interesting candidate, as it is required for JNK signaling and can be activated by tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) at the level of TGF-β receptor type I (Mu et al., 2012). Furthermore, TRAF6 has recently been shown to interact with the β1 subunit of α3β1 integrin (Yazlovitskaya et al., 2015).

The role of α11β1 in skin fibrosis is currently unknown but it has been shown to have a pro-fibrotic role in diabetic cardiomyopathy, a condition in which high levels of glucose lead to the glycation of collagen, resulting in heart fibrosis. In an experimental rat model of diabetic cardiomyopathy, the interaction of cardiac fibroblasts with glycated collagen through α11β1 increased TGF-β2 expression, which in turn induced the expression of alpha-smooth muscle actin (α-SMA) (Talior-Volodarsky et al., 2012). Interestingly, glycation appears to interfere with α11β1-mediated adhesion to collagen, while still stimulating myofibroblast differentiation (Talior-Volodarsky et al., 2015). The increased level of α11 under these conditions has been interpreted as an attempt by the cells to compensate for reduced adhesion. In the diabetes models, TGF-β2 is responsible for the increased expression of α11β1 that is induced by the binding of Smad3 to a site within the *ITGA11* promoter that is distinct from the site that has previously been described to mediate TGF-β1-stimulated gene expression of α11 (Lu et al., 2010; Talior-Volodarsky et al., 2015).

One important role for α11β1 in tumorigenesis was first suggested in 2002, when Wang et al. identified this integrin as a new biomarker for non-small-cell lung cancer (NSCLC) (Wang et al., 2002). Using representational difference analysis, they showed that its gene *ITGA11* is overexpressed in lung adenocarcinoma as compared with healthy lung tissue. Later, it became clear that α11β1 is essentially overexpressed in the stroma of NSCLC, especially in CAFs (Navab et al., 2011; Zhu et al., 2007). A role for α11β1 in tumorigenesis has been indicated in xenograft experiments where the mixing of tumor cells with α11-expressing fibroblasts was shown to stimulate tumor growth. In a different model, involving 3D heterospheroids composed of MEFs and lung carcinoma cells, a downregulation of the chemokine CXCL5 within the tumor cells in the absence of α11 has been observed, suggesting that α11-expressing fibroblasts stimulates the autocrine secretion of CXCL5 in NSCLC cells (Lu et al., 2014) (Fig. 2). However, this is not the only role of α11β1 in tumorigenesis – as indicated by our recent study that emphasizes the ability of α11β1 to remodel collagen matrices during wound healing (Schulz et al., 2015). In the heterospheroid model, fibroblasts synthesize collagen I independently of α11 but, only α11-expressing fibroblasts are able to induce contraction of the collagen matrix. This reorganization of the matrix resulted in an increase in interstitial fluid pressure (Lu et al., 2014), forming a barrier to drug delivery. In another recent study, a NSCLC xenograft model has been described, in which α11β1-promoted collagen remodeling, and a correlation between tumor tissue stiffness and α11 expression was observed (Navab et al., 2015). Here, a reduced activation of FAK and ERK in tumors grown with in α11-deficient mice was also noted. An analysis of possible genes involved in regulating tissue stiffness directly or indirectly revealed a correlation between stromal α11 expression and LOXL1, an elastin and collagen cross-linking enzyme (Navab et al., 2015). As α11 is selectively expressed on fibroblasts, it is not surprising that its mRNA is up-regulated by EMT-like events in various tumor models (Fernando et al., 2010; Ke et al., 2008). So far, this induction of α11 mRNA has not been confirmed to translate to the protein level, and it is thus not yet known whether α11β1 affects the EMT process (Fig. 2). Recently, however, *ITGA11* was identified as an invasion-promoting gene within a seven-gene signature that had been established for the leading invasive 'trailblazer' cells in a spheroid-based model for collective invasion of breast cancer cells (Westcott et al., 2015). These data indicate that the role of α11 in tumors is not restricted to CAFs but could also extend to tumor cells that assume a mesenchymal invasive phenotype (Fig. 2). The roles of the individual collagen-binding integrins in wound healing, fibrosis and tumors are summarized in Table 1.

The receptor-ligand paradox: collagen-binding integrins – receptors in search of a function?

We now have substantial detailed and data on the structure and function of integrins, their mechanism of activation and their roles in different biological processes but – as outlined above – in the field of cell-collagen adhesion, one paradox remains: why are phenotypes of individual organisms that lack certain collagens not phenocopied when the corresponding collagen receptors are defective (Zeltz et al., 2014)?

The trait that distinguishes collagens from other matrix ligands is, of course, that collagens are the most abundant proteins in the vertebrate body and that they assume a central structural role in forming the framework for connective tissues. This poses an enormous challenge when trying to analyse the functions of the 28 members of the collagen family that depend on collagen-binding cell-surface receptors. Some of the relevant issues when considering why mice deficient in collagen-binding integrins show only mild

phenotypes include redundancy, compensation, alternative attachment mechanisms and type of animal model (see Box 2).

Taken together, our current knowledge of collagen receptors suggests that they have limited roles during static tissue homeostasis events but appear to be more important for dynamic events that occur during tissue damage, regeneration and inflammation. This identifies collagen receptors as interesting biomarkers and prognostic and/or therapeutic disease targets as discussed below.

Collagen-binding integrins in wound healing and tissue regeneration

The recent finding that α11β1 mediates collagen remodeling in the healing wound has raised a number of questions. Lineage tracing studies have clearly demonstrated the existence of distinct subsets of cells in the dermis, such as papillary, reticular and adipocyte precursor cells (Driskell et al., 2013). Other experiments have shown that the deletion of fibroblasts that express engrailed-1 leads to scarless wound healing (Rinkevich et al., 2015). Thus, it is important to determine which subset of dermal fibroblasts expresses α11.

A fundamental problem in diabetes is ulcer formation and delayed wound healing (Schultz et al., 2011). In this context, with the aim to improve the healing of chronic wounds, it would be interesting to modulate collagen-binding integrin activity.

Box 2. Hypotheses to explain weak knockout phenotypes of collagen-binding integrin

Redundancy within the subfamily of collagen-binding integrins. There is currently no genetic model that allows to analyze the deletion of the entire subfamily of collagen-binding integrins. However, there is no striking overlap of the expression patterns of the collagen-binding integrins as, for example, in platelets. Although fibroblasts express α1β1, α2β1 and α11β1, mice that lack both α2 and α11 show a minimal additional phenotype when compared with individual knockouts (Blumbach et al., 2012; Schulz et al., 2015). Thus, the hypothesis that collagen-binding integrins have redundant functions is a less likely explanation for the weak phenotypes observed.

Compensation mechanisms. Multiple examples demonstrate that the acute block of protein function by using antibodies (without any opportunity for the cells to compensate) can have effects that differ from those seen in genetic knockouts, in which the cell or organism has had a chance to activate compensatory mechanisms. To, more thoroughly, test the combined roles of α2 and α11 under conditions of minimal compensation, it would be interesting to conditionally delete α2 and α11 in a fibroblast-specific manner. The compensation mechanism is, thus, a possible scenario, but one that might be difficult to prove experimentally.

Alternative attachment mechanisms during development. Alternative mechanisms of attachment of integrin to collagen exist during development, and receptors involved in this process have other roles than just the organization of tissue structure. Some of the non-integrin receptors may take over this function in the absence of collagen-binding integrins, although our understanding of the roles non-integrin collagen receptors have as mechanolinks is limited. An attractive hypothesis is that the fibrils in mature collagen matrices are so tightly packed that there is only a limited availability of integrin-binding sites. This would enable the anchoring of cells to the collagen matrices through COLINBRI-mediated adhesion (Zeltz et al., 2014) and is a likely scenario.

Choice of model organism. The mouse is not the optimal organism for analysing cell–collagen interactions in the musculoskeletal system, in that the role of collagen-binding integrins might be underestimated – as illustrated by the severe chondrodysplasia in dogs with an α10-truncating mutation (Kyöstilä et al., 2013).

In view of the restricted distribution of α10β1 in cartilage, it is possible that reagents that stimulate α10β1 have beneficial effects on cartilage physiology. It should, thus, be possible to conduct experiments focusing on regenerative medicine that take advantage of the fact that α10β1 identifies chondrogenic mesenchymal stem cells to achieve the best result of tissue replacement for relevant groups of patients suffering from osteoarthritis and rheumatoid arthritis.

Collagen-binding integrins in the tumor stroma

The collagen matrices laid down during embryogenesis are, in general, thought to be accessible to cells. As these matrices mature in the adult they are crosslinked and many of the interaction sites in the monomeric molecules become occupied by interacting proteins. Turnover rates of fibrillar collagens are generally low, with the periodontal ligament representing an exception (Sodek and Ferrier, 1988), but the cell–collagen interactions show a dynamic relationship during tissue regeneration events, such as wound healing, when fibroblasts of various origins are recruited and produce a wound matrix that is rich in fibrillar collagens (Schäfer and Werner, 2008). These include collagen type III with a smaller fibril diameter that, as the granulation tissue matures, is replaced with collagen I (Merkel et al., 1988). In fibrosis, overproduction of fibrillar collagen causes tissue dysfunction, but the role of the fibrillar collagen-rich tumor stroma is still a matter for debate. Experimental tumor models suggest that fibrillar collagens contribute to tumor growth and metastasis (Provenzano et al., 2009, 2008; Xiong et al., 2014). Furthermore, artificial crosslinking of collagens by overexpression of LOX has been shown to stimulate tumor growth in an artificial breast cancer model (Levental et al., 2009). In numerous models, the rearranged linearized collagen that is observed in some tumors appears to offer tracks for metastasizing tumor cells, but the possible role of collagen-binding and COLINBRI-binding integrins in these processes is not sufficiently well understood to therapeutically target them (Provenzano et al., 2006, 2009).

Concluding remarks

On the basis of our current understanding, collagen-binding integrins have a modest function with respect to normal tissue homeostasis: α2β1 affects thrombus formation, α10β1 appears to be important for cartilage formation and α11 for tooth eruption. However, under disease conditions, such as in inflammation, tissue regeneration events and tumors, collagen-binding integrins play a more-prominent role.

Integrins α1β1 and α2β1 might be needed for a correct and innate immune response in various populations of immune cells, whereas α10β1 and α11β1 appear to be central to how connective tissue cells perform in the musculoskeletal system. Recent data suggest that α11β1 is a main collagen receptor for collagen remodeling on activated fibroblasts in wounds, fibrotic tissues and the tumor stroma. With the growing realization that fibroblasts and mesenchymal stem cells are important modulators of tissue regeneration events, integrins α10β1 and α11β1 are promising molecular targets for modulating regenerative events (wound healing, cartilage repair), as well as for pathological processes (osteoarthritis, fibrosis, tumor spread). Both integrins might be excellent biomarkers for chondrocyte-specific and fibroblast-specific processes.

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