Integrin β1 in Pancreatic Cancer: Expressions, Functions, and Clinical Implications

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Simple Summary: Pancreatic cancer (PC) is a highly aggressive malignant tumor with an extremely poor prognosis. Early diagnosis and treatment are key to improving the survival rate of PC patients. Emerging studies show that integrins might contribute to the pathogenesis of PC. This review presents the various signaling pathways that are mediated by integrins in PC and emphasizes the multiple functions of integrin β1 in malignant behaviors of PC. It also discusses the clinical significance of integrin β1 as well as integrin β1-based therapy in PC patients.

Abstract: Pancreatic cancer (PC) is characterized by rapid progression and a high mortality rate. The current treatment is still based on surgical treatment, supplemented by radiotherapy and chemotherapy, and new methods of combining immune and molecular biological treatments are being explored. Despite this, the survival rate of PC patients is still very disappointing. Therefore, clarifying the molecular mechanism of PC pathogenesis and developing precisely targeted drugs are key to improving PC prognosis. As the most common β subunit of the integrin family, integrin β1 has been proved to be closely related to the vascular invasion, distant metastasis, and survival of PC patients, and treatment targeting integrin β1 in PC has gained initial success in animal models. In this review, we summarize the various signaling pathways by which integrins are involved in PC, focusing on the roles of integrin β1 in the malignant behaviors of PC. Additionally, recent studies regarding the feasibility of integrin β1 as a diagnostic and prognostic biomarker in PC are also discussed. Finally, we present the progress of several integrin β1-based clinical trials to highlight the potential of integrin β1 as a target for personalized therapy in PC.

Keywords: integrin β1; pancreatic cancer; signaling pathways; targeted drugs

1. Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death worldwide and is characterized by rapid progression, high invasiveness, and resistance to chemotherapeutic agents [1,2]. More than 80% of the PC lesions have invaded surrounding lymph
nodes and might even develop distant metastasis [3]. In theory, the possibility of surgical resection in these patients has been lost and only chemotherapy and palliative care are possible. Due to the complex anatomical position of the pancreas, PC surgery is often more complex than other tumors and cannot completely remove the lesions [4]. Additionally, even if the patients undergo surgical treatment, the postoperative recurrence rate is high, and the median survival time after radical surgery is only 18 months [5]. Despite advances in PC diagnosis and combination therapy of PC over the years, the overall 5-year survival rate remains below 5%, and the median survival time is only close to 6 months [6,7]. Therefore, targeting the invasion and metastasis of tumor cells is a cutting-edge research area and an urgent issue in PC.

Tumor cells are endowed with the following characteristics: sustained activation of intracellular proliferation signals, decreased effects of tumor suppressors, resistance to cell apoptosis, immune evasion, enhanced tumor angiogenesis, and strong abilities of invasion and metastasis [8]. The main reason for the poor prognosis of PC stems from the biological characteristics of early local invasion and distant metastasis of PC cells, which could be regulated by extracellular matrix (ECM) components [9]. One of the main clinicopathological features of PC is the existence of a large amount of fibrous tissue and abundant ECM around tumor cells [10]. Studies have shown that these special ECM components can not only provide physical support and protection to the tissue but also regulate the invasion and metastasis of PC by interacting with ECM receptors on PC cells [11–14]. Among those ECM receptors, integrins, the most extensively studied family, play an important role in controlling signal transduction during ECM–PC cell communications. This review will summarize the current knowledge about integrins, emphasizing integrin-mediated signaling pathways in PC, such as the outside-in and inside-out signaling. In particular, we will focus on the roles of the β1 subunit in the occurrence and development of PC and present strategies targeting integrin β1 for researching PC diagnostics and treatment.

2. Signaling Pathways Mediated by Integrins in PC

Integrins, a transmembrane glycoprotein molecule, are one of the members of the cell surface adhesion molecule family, and their primary biological role is to mediate cell-to-cell and cell-to-ECM interaction [15–17]. Regarding the structure, integrins respond specifically to ECM signals under different physiological/pathological conditions through their unique transmembrane bimolecular subunits α and β [18]. Up to now, 18 α and 8 β subunits have been reported in mammalian cells, forming 24 different integrins [19,20]. Among them, the subfamily composed of αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, α5β1, α8β1, and α11β3 is the most widely researched. Members of this subfamily can recognize the specific Arg-Gly-Asp (RGD) short peptide, which diffusely exists in the ECM rich in fibronectin, vitronectin, osteopontin, and fibrinogen [21]. Another subfamily consists of α1β1, α2β1, α3β1, α4β1, α6β1, α7β1, α10β1, α11β1, and α6β4, and exerts the effects by specifically recognizing collagen or laminin molecules in the ECM [22]. The conduction of integrin-mediated signal transduction needs the cooperation of α and β subunits, wherein the α subunit mainly recognizes specific ECM molecules. In contrast, the β subunit is responsible for transducing related cell signals. Abnormal expression of α or β subunits, or alterations in their synergistic effect, can lead to the occurrence and development of tumors [23,24]. Studies have shown that cancer cells obtain multiple biological behaviors in epithelial-derived solid tumors by expressing different integrins. In PC, various integrins have been reported to drive epithelial–mesenchymal transition (EMT), induce cancer stem cells (CSCs), facilitate metastasis, and promote treatment resistance. For example, PC cells are known to regulate CSC adhesion by expressing integrin α6 and β3; integrin αvβ3 can promote PC stemness and drug resistance and is a marker for PC [25]. As for tumor metastasis, integrin β3 was found to increase anchorage-independent cancer cell proliferation, thereby accelerating metastatic formations growth of PC [26,27]. Regarding radiochemoresistance, Jin et al. identified β8 integrin in three-dimensional (3D), ECM-based
cell cultures as a potent therapeutic target for PC, and the mechanism involves integrin β8-induced autophagy upon irradiation [28]. Based on these fundamental research, targeted strategies have been explored for PC treatment. Moore et al. unveiled that peptide–drug conjugate SG3299, developed from foot-and-mouth disease virus, showed αvβ6-selectivity in vitro and in vivo and could specifically eliminate αvβ6-positive cancer cells, representing a promising approach for PC therapy [29]. Another phase I clinical trial utilized an αvβ3 targeting protein to selectively deplete cancer-associated pancreatic stellate cells, enhancing drug delivery and gemcitabine efficacy in PC by suppressing tumor angiogenesis [30].

The following section lists the main signaling pathways mediated by integrins in PC (Figure 1).

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**Figure 1.** Signaling pathways mediated by integrins in PC cells. Integrins are heterodimeric cell-surface proteins consisting of α and β subunits. They have both inactive and active conformations that determine their binding affinities for ECM ligands (e.g., collagen I, collagen IV, fibronectin). Inactive integrins are always bent with physiological low-affinity, whereas active integrins are in an extended state with high-affinity and exhibit the separation of α and β lower legs. Active integrins recruit the adapter talins and, subsequently, activate FAK and Src. FAK/Src complex recruits and phosphorylates p130Cas and paxillin, and then induces the activation of downstream signaling, including Rac, Cdc42, and Rho, which are crucial regulators of cytoskeletal reorganization. This process can transmit information on their ligands’ chemical identity and physical state into cells, called the outside-in signals. Integrin adhesion can also crosstalk with other RTK pathways to regulate cell migration, survival, and growth. Additionally, integrins respond to inside-out signals by regulating protein interactions at the cytoplasmic tail region of integrins and modulating the strength of cell adhesion.
2.1. Bidirectional Signaling Transduction Controls the Coupling of Ligands with Cytoskeleton and the Formation of Focal Adhesion

As the main ECM receptor molecule on the cytomembrane, integrins activate key signaling intracellular molecules through the interaction with various ECM molecules, thereby regulating the expression of related genes and, ultimately, mediating biological behaviors such as cell proliferation, differentiation, movement, and migration, which are the so-called outside-in signals. The outside-in signaling refers to the fact that integrins bind to ligands in clusters and affect intermolecular or intramolecular connections inside the cell. With initial ligand binding, more and more adaptor proteins such as focal adhesion kinase (FAK) are recruited to the integrin cytoplasmic tail. They are phosphorylated, thereby progressively strengthening the focal adhesions. FAK associates with proto-oncogene tyrosine–protein kinase Src and becomes active. In the context of extracellular matrix adhesion, such plaques are called “cell-matrix adhesion” [31]. Integrin-mediated activation of the FAK/Src complex can control the activation of Rho family members, which are crucial regulators of cytoskeletal dynamics [32]. The activated FAK/Src complex first recruits and phosphorylates p130Cas, and then phosphorylated p130Cas recruits Dock180 and engulfment and cell motility (ELMO) through the adaptor protein Crk. The Dock180/ELMO complex can act as a guanine exchange factor (GEF) for Rac [33]. Rac GTPase is essential for Arp2/3-mediated growth of branched-chain F-actin, which drives membrane protrusions in the form of lamellipodia. Another cell-matrix adhesion protein, paxilin, can be phosphorylated by the FAK/Src complex. Paxilin recruits paxilin kinase linker (PKL) and Pak interacting exchange factor (PIX), two GEFs of Rac and Cdc42 (another Rho GTPase that drives filopodia elongation) [34,35]. However, when an external force is applied to integrins, FAK cooperates with another Src family kinase, Fyn, to activate two GEFs of RhoA, leukemia-associated RhoGEF (LARG) and GEF-H1, to enhance the contractility of the cytoskeleton, resulting in the reinforcement of the cell [36]. By coordinating the activity of Rho GTPases and the recruitment of components of the actin polymerization machinery, such as Arp2/3, the integrin-mediated adhesion complex is a signaling hotspot for the regulation of cytoskeletal dynamics. The inside-out signaling pathway is the intracellular signaling pathway that regulates protein interactions at the cytoplasmic tail region of integrins, which induce conformation changes in integrin extracellular domains. The inside-out signaling is regulated by talins and kindlins, [37], as well as the dephosphorylation and O-GlcNAcylation of the focal adhesion complexes [38]. In detail, talins and kindlins use the four-point-one, ezrin, radixin, and moesin (FERM) domain to connect with the tail of the integrin and trigger its conformational change for activation by separating the tail. If intracellular signaling disrupts intramolecular interactions within talins, the interaction between talins and integrins can be affected. The mode of regulation of kindlins is still unclear, and the coordinated behaviors of the two proteins are also illusive. Apart from talins and kindlins, the lateral diffusion and aggregation of integrins itself can further regulate cell adhesion strength [39]. In PC, many integrins have been reported to contribute to focal adhesion formation. For example, collagen I can facilitate adhesion, accelerate motility, and stimulate trans-migration through integrin α2β1. Mechanistically, collagen I induces the formation of F-actin and focal adhesions in PC cells, which is mediated by increased phosphorylation and subsequent activation of FAK signaling [40].

2.2. Integrins Are a Bidirectional Pressure Signal Transmitter

Integrins and some cell-matrix adhesion-related proteins could act as pressure sensors [41,42]. Extracellular stress is transmitted via integrins to the cytoplasmic proteins attached, thereby exposing binding sites for intracellular interactions. In response to pressure, a series of conformational changes occur in integrins, and related proteins present in cell-matrix adhesion are activated, including FAK, p130Cas, vinculin, etc. In turn, intracellular stress can also change the conformation of the integrin-related protein complex, allowing integrins to pull proteins such as fibronectin in the ECM. This may lead to solidification of the ECM, and once binding sites are exposed, more interactions between fibronectin...
molecules may occur during fibril formation or collagen network remodeling [43,44]. Thus, integrins allow cells to balance intracellular cytoskeleton contractility and extracellular matrix solidification. Zeltz et al. found that integrin α11 expression is upregulated in PC and demonstrated a moderate level of α11+ in myofibroblastic cancer-associated fibroblasts (myCAFs) associated with PC tumors. Using a function-blocking α11 antibody to inhibit cell adhesion to collagen I could hinder fibroblast-mediated collagen remodeling and delay the 3D migration rates of PC myCAFs. These results suggest that interaction between integrins and ECM is an essential factor during the process of collagen remodeling [45].

2.3. Crosstalk with Other Receptors in Inside-Out Signaling Pathways

The above-described integrin-regulated signaling pathways are not independent but act synergistically with signaling from other receptors. In fact, a major part of integrin signaling may involve the activation of other downstream receptor pathways. One of the earliest examples of this concept came from the study of the adhesion control of the Rac small GTPases. It has been shown that activating Rac in response to cell adhesion requires epidermal growth factor receptor (EGFR) signaling [46]. In this context, the ability of integrins to aggregate key enzymes, including kinases and GTPases and corresponding substrates, could trigger growth factor signaling through these enzymes. However, it is now evident that integrin-mediated adhesion can more directly lower the threshold for receptor tyrosine kinase (RTK) activation. Integrins can associate with several RTKs, including EGFR, insulin-like growth factor one receptor (IGF-1R), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), hepatocyte growth factor receptor (HGFR/cMet), and macrophage stimulating one receptor (MST1R, Ron). In some studies, this integrin-RTK crosstalk has been proved to be mediated by Src family kinases [47,48].

Integrin-mediated adhesion to the ECM can enhance growth factor signaling in another way. Many growth factors are associated with heparin or heparan sulfate found in ECM proteoglycans [49]. Proteolytic cleavage of ECM proteins can release growth factors to bind to receptors, and, in some cases, interactions with the ECM have been found to contribute to the efficient presentation of growth factors to their receptors. ECM proteins also contain growth factor-like motifs such as TGFβ. In its inactive form, TGFβ is bound and masked by latency-associated peptide (LAP). Integrin αv can interact with the RGD motif in LAP and causes the exposure of activated TGFβ, which subsequently binds and activates the TGFβ receptor. Interestingly, this can occur through different protease-dependent or protease-independent mechanisms, the latter involving the integrin’s traction forces exerted on the TGFβ–LAP complex by the actin cytoskeleton [50,51]. Recent studies show that high expression of integrin αv in PC cells is associated with reduced survival in patients, and the knockdown of integrin αv in PC cells massively restrains primary tumor growth, peritoneal carcinomatosis, and pulmonary metastasis. The mechanism behind it demonstrates that integrin αv could activate latent TGFβ and thereby drives EMT [52]. Additionally, integrin αv is upregulated in macrophages and promotes the stemness of PC cells. Mechanistically, macrophage-expressed integrin αv facilitates the acquisition of stemness properties of PC cells by regulating the TGFβ/Smad2/3 pathway. These data indicate that strategies targeting the interaction between integrins and other receptors might be a new therapeutic modality for PC [53].

2.4. Control Signaling by Anchoring and Regulating the Cytoskeleton

By anchoring and regulating the cytoskeleton, integrins contribute to gene transcription while conceiving and responding to mechanical forces. This response can be achieved by altering the concentrations of second messengers such as calcium and cyclic adenosine and crosstalk with the growth factor receptor signaling pathway, as mentioned above [54]. More directly, the cytoskeleton is linked to integrins on the plasma membrane as well as the nuclear membrane through linkers of the nucleoskeleton and cytoskeleton (LINC) complex. Here, the nesprin proteins in the outer membrane connect to microtubules, actin
fibers, and intermediate filaments, while the SUN protein in the inner membrane binds to the nuclear lamina. Since chromatin-binding proteins and DNA are attached to the nuclear layer, extracellular mechanical stress may be propagated to chromatin and cause gene expression through conformational modifications of DNA and related proteins [55]. However, currently, direct evidence demonstrating a purely mechanical coupling between the ECM and gene expression is still lacking. In a previous study, integrin α2 was shown to be overexpressed in PC and promoted the proliferation and invasion abilities of cancer cells. RNA-seq assays indicated that integrin α2 transcriptionally regulated the expression of PD-L1 in PC, which was further shown to be mediated by the STAT3 pathway [56]. Thus, interfering with integrin-mediated gene transcription such as PD-L1 is a feasible method to enhance the efficacy of checkpoint immunotherapy against PC.

3. An Overview of Integrin β1

Integrin β1, also known as CD29, is a human protein-coding gene with a full length of 58048bp. Located on human chromosome 10p11.2 with a total of 18 exons, it has three transcript variants named transcript variants 1A, 1E, and 1D. Transcript variant 1A has a full length of 3735bp with 16 exons, and encodes a protein of 798 amino acids; transcript variant1E has a full length of 3794bp and encodes a protein of 798 amino acids; transcript variant1D has a full length of 3739bp and encodes a protein of 801 amino acids [57].

As the most common β subunit of the integrin family, integrin β1 is currently known to bind to different α subunits to form 11 different integrins. Among these, integrin β1 forms integrins very late antigen (VLA)-1 to 6, α7β1, α8β1, and αvβ1 (vitronectin receptor, VNR) with integrins α1 to α8 and αv subunits, respectively, constituting the VLA family of integrins, which is widely distributed throughout the body [58]. A series of studies have unveiled that integrins composed of β1 subunit play a key role in maintaining the stemness property of tumor cells as well as promoting tumor metastasis and chemotherapy/radiation resistance by participating in the transduction of various intracellular signaling pathways [59–65]. In PC, the β1 subunit has been closely related to the vascular invasion, distant metastasis, and survival of the patients, and treatment targeting integrin β1 in PC has gained initial success in animal models [66]. Table 1 summarizes the studies regarding integrin β1 in PC.
| No. | Integrin | Year | Cell Lines | Expression | Functions | Mechanism | Model Used | Reference PMID |
|-----|----------|------|------------|------------|-----------|-----------|------------|----------------|
| 1   | β1      | 2005 | MIA PaCa-2, PaCa-3 | up         | +         | +         | +          | 12855298      |
| 2   | β1      | 2005 | SW1990, Capan-2 | up         | +         | +         | +          | 15949051      |
| 3   | α4β1    | 2006 | PaCa-3, Capan-2, SW1990 | up         | +         | +         | +          | 16540403      |
| 4   | β1      | 2006 | MIA PaCa-2, PaCa-3 | up         | +         | +         | +          | 16547950      |
| 5   | β1      | 2006 | Panc-1, BxPC-3 | up         | +         | +         | +          | 16554147      |
| 6   | β1      | 2007 | PaCa-3, PaCa-2, PaCa-1 | up         | +         | +         | +          | 17147122      |
| 7   | β1      | 2007 | Capan-1 | up         | +         | +         | +          | 17352016      |
| 8   | β1      | 2006 | BxPC-3, PaCa-1, SW1990 | up         | +         | +         | +          | 17728289      |
| 9   | β1      | 2007 | PaCa-1 | up         | +         | +         | +          | 17748146      |
| 10  | β1      | 2006 | MIA PaCa-2, MIA PaCa-3, PaCa-1 | up         | +         | +         | +          | 19741815      |
| 11  | β1      | 2006 | MIA PaCa-2 | up         | +         | +         | +          | 19825366      |
| 12  | β1      | 2010 | MIA PaCa-2 | up         | +         | +         | +          | 20157415      |
| 13  | β1      | 2013 | BxPC-3, MIA PaCa-2 | up         | +         | +         | +          | 21459421      |
| 14  | β1      | 2013 | PaCa-3, Colo-357, AsPC-1, BxPC-3, MIA PaCa-3, PaCa-1 | up         | +         | +         | +          | 21583820      |
| 15  | β1      | 2013 | PaCa-1, PSN-1, MIA PaCa-2 | up         | +         | +         | +          | 21648992      |
| 16  | β1      | 2014 | PaCa-2 | up         | +         | +         | +          | 21674943      |
| 17  | β1      | 2014 | PaCa-1, PSN-1 | up         | +         | +         | +          | 22052313      |
| 18  | β1      | 2014 | PaCa-1, BxPC-3 | up         | +         | +         | +          | 23225050      |
| 19  | β1      | 2014 | PaCa-1, BxPC-3 | up         | +         | +         | +          | 23353271      |
| 20  | β1      | 2012 | Par-3 | up         | +         | +         | +          | 22704436      |
| 21  | β1      | 2012 | PT45-P1 | up         | +         | +         | +          | 22737971      |
| 22  | β1      | 2013 | Colo-357, Panc-1, Panc-MUC1 | up         | +         | +         | +          | 23734791      |
| 23  | α2β1    | 2014 | PaCa-1, UlaPaCa | up         | +         | +         | +          | 24201748      |
| 24  | β1      | 2014 | PaCa-3, MIA PaCa-2, MIA PaCa-3, AsPC-1, BxPC-3, CFPAC-1, Panc-1, MIA PaCa-2 | up         | +         | +         | +          | 24460796      |
| 25  | β1      | 2014 | PaCa-1, BxPC-3, CFPAC-1, Panc-1, MIA PaCa-2 | up         | +         | +         | +          | 24460796      |
| 26  | β1      | 2014 | MIA PaCa-2, MIA PaCa-3, AsPC-1, Panc-1 | up         | +         | +         | +          | 24720337      |
| 27  | β1      | 2014 | MIA PaCa-2, MIA PaCa-3, AsPC-1, Panc-1 | up         | +         | +         | +          | 24844210      |
| 28  | α2β1    | 2014 | BxPC-3, Capan-1, Panc-1, MIA PaCa-2 | up         | +         | +         | +          | 25215922      |
| 29  | α2β1    | 2014 | BxPC-3, Capan-1, Panc-1, MIA PaCa-2 | up         | +         | +         | +          | 25336083      |
| 30  | α2β1    | 2015 | AsPC-1, Capan-1, SU86.86, Panc-1, AsPC-1, Capan-1, SU86.86 | up         | +         | +         | +          | 25354493      |
| 31  | β1      | 2016 | AsPC-1, Capan-1, SU86.86, Panc-1 | up         | +         | +         | +          | 25465987      |
| 32  | β1      | 2016 | PSC | up         | +         | +         | +          | 26769062      |
| 33  | β1      | 2016 | MIA PaCa-2, ASC-1, MIA PaCa-2, ASC-1 | up         | +         | +         | +          | 27170258      |
| 34  | β1      | 2017 | BxPC-3, Capan-2, BxPC-3, Capan-2, SW1990 | up         | +         | +         | +          | 27286233      |
| 35  | β1      | 2017 | PaCa-1, UlaPaCa | up         | +         | +         | +          | 27795776      |
| 36  | β1      | 2017 | PaCa-1, BxPC-3, CFPAC-1, Panc-1, MIA PaCa-2 | up         | +         | +         | +          | 28416805      |
| 37  | β1      | 2017 | MIA PaCa-2, Capan-1, MIA PaCa-2 | up         | +         | +         | +          | 28560430      |
| 38  | α2β1    | 2018 | PaCa-1, UlaPaCa | up         | +         | +         | +          | 28652661      |
| 39  | β1      | 2018 | PaCa-1, BxPC-3, Panc-1 | up         | +         | +         | +          | 28916526      |
| 40  | β1      | 2018 | PSC | up         | +         | +         | +          | 29070928      |
| 41  | β1      | 2018 | MIA PaCa-2, Capan-1, Panc-1, MIA PaCa-2 | up         | +         | +         | +          | 29277908      |
| 42  | β1      | 2019 | VASP | up         | +         | +         | +          | 29572721      |
| 43  | β1      | 2018 | PaCa-1, SW1990, MIA PaCa-2 | up         | +         | +         | +          | 29998460      |

Table 1. Overview of cellular functions of reported β1 integrins in pancreatic cancer.
| No. | integrin | Year | Cell Lines | expression | functions | mechanism | model used | reference PMID |
|-----|----------|------|------------|------------|-----------|------------|------------|----------------|
| 44  | β1       | 2018 | Panc-1     | up         | Proliferation, Cell Cycle, Apoptosis, Angiogenesis, Adhesion, Migration, Invasion, CSC | + integrin β1/CD44 | cell | 30244540 |
| 45  | β1       | 2018 | AsPC-1     | up         | +          | +          | +          | cell | 30244573 |
| 46  | β1       | 2018 | Panc-1, PK59 | up         | +          | +          | +          | cell | 30410872 |
| 47  | β1       | 2019 | Capan-1, JPC-3 | up         | +          | +          | +          | cell | 30739724 |
| 48  | α1β1     | 2019 | Mia PaCa-2, MIA PaCa-2, CFPAC-1, BxPC-3, Panc-1, AsPC-1, Sb199, AsPC-1, Panc-1, BxPC-3 | up         | +          | +          | +          | cell | 31190418 |
| 49  | α5β1     | 2019 | Mia PaCa-2 | up         | TGF-β1/TFEB/RAB1A/α5β1, endocytosis | +          | +          | cell | 31357652 |
| 50  | α1β1     | 2019 | Mia PaCa-2 | up         | +          | +          | +          | cell | 31452807 |
| 51  | α1β1     | 2019 | Mia PaCa-2 | up         | +          | +          | +          | cell | 31607226 |
| 52  | α3β1     | 2020 | AsPC-1, Mia PaCa-2, BxPC-3, Mia PaCa-2 | up         | +          | +          | +          | cell | 31711924 |
| 53  | α3β1     | 2020 | AsPC-1, Mia PaCa-2, BxPC-3, Mia PaCa-2 | up         | HLA-B/Integrin β1, Integrin β1 and Heparan Sulfate, Dual-Targeting/VAP | +          | +          | cell | 32194056 |
| 54  | α1β1     | 2020 | PanC-1     | up         | +          | +          | +          | cell | 32268681 |
| 55  | α1β1     | 2020 | iKras/p53* PC cells | up         | +          | +          | +          | cell | 32816409 |
| 56  | α1β1     | 2020 | Panc-1     | up         | +          | +          | +          | cell | 33006527 |
| 57  | α5β1     | 2020 | Panc-1     | up         | +          | +          | +          | cell | 33550776 |
| 58  | α1β1     | 2020 | Panc-1     | up         | +          | +          | +          | cell | 33550776 |
| 59  | α1β1     | 2020 | Panc-1, Mia PaCa-2 | up         | +          | +          | +          | cell | 33550776 |
| 60  | α1β1     | 2020 | Mia PaCa-2 | up         | +          | +          | +          | cell | 34435355 |
| 61  | α1β1     | 2020 | Mia PaCa-2 | up         | +          | +          | +          | cell | 34698957 |
| 62  | α1β1     | 2022 | adipose-derived mesenchymal stem cells | up         | +          | +          | +          | cell | 35216699 |
| 63  | α1β1     | 2022 | CF Pac-1, ST21990 | up         | +          | +          | +          | cell | 33541675 |

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*α* indicates that the integrin plays a role in related cancer cell biological functions. *iKras*p53* refers to PC cells derived from transgenic mice "iKras*p53* mice".
4. Roles of Integrin β1 in the Malignant Behaviors of PC

4.1. Integrin β1 and Proliferation-Related Signaling

Integrins are critical for cell proliferation under physiological and pathological conditions [67]. As for the behind mechanism, interactions between integrins and growth factor receptors (GFR) have drawn increasing attention these years. In normal cells, diverse receptors including EGFR, cMet, PDGFR, and VEGFR can interact with integrins to activate cell proliferation activity. Previous studies found that integrins could directly activate EGFR in normal endothelial cells independent of EGF. Experiments in liver regeneration demonstrated that the downregulation of the β1 subunit in hepatocytes decreased c-Met and EGFR phosphorylation, thereby inhibiting cell proliferation [68,69]. In tumor cells, integrins also play a part in cell proliferation by interacting with GFR [70]. In vivo/in vitro experimental studies discovered the interaction between EGFR and integrin α5 as well as integrin β1 in tumors [71,72]. Studies in hepatoma have found that the cellular macromolecular protein cysteine-rich protein 61 (CYR61/CCN1) can stimulate the accumulation of reactive oxygen species (ROS) in cells by interacting with integrin α6β1, thereby inhibiting the activation of the EGFR signaling pathway and the proliferation of hepatoma cells; in addition, using siRNA to interfere with the expression of the integrin β1 subunit could effectively suppress the viability of hepatoma cells [73,74]. Regarding PC, overexpression of integrin β1 and the downstream Src-AKT activation have been reported. This triggers an EGFR ligand-independent proliferation signaling, bypassing the EGFR-blocking effect, and mediates resistance to the anti-EGFR monoclonal antibody, cetuximab. Knockdown of integrin β1 or inhibition of Src or AKT can successfully re-sensitize cetuximab-resistant (CtxR) PC cells to cetuximab. The researchers then discovered that neuropilin-1 (NRP1) physically interacted with active integrin β1, but not the inactive one on the cell surface. They generated an EGFR and NRP1 dual targeting antibody, Ctx-TPP11, to simultaneously inhibit active integrin β1-driven signaling and suppress EGFR signaling. Further experiments proved the efficacy of Ctx-TPP11 on the inhibition of PC proliferation, both in vitro and in vivo. This study offered an effective therapeutic strategy based on EGFR and integrin β1 dual targeting, which might become a hot topic in PC therapy [75].

4.2. Integrin β1 and Tumor Suppressor p53

Numerous studies have reported the inactivation of the tumor suppressor protein p53 in different forms of human cancer [76]. It is believed that the leading cause for the inactivation of the wild-type p53 signaling pathway in tumor cells is the deletion mutation of the p53 gene or abnormal upregulation of its inhibitory proteins, among which integrins play an indispensable role [77,78].

Previous literature demonstrates that tumor cells can suppress p53 activation through integrin α5β1 in response to chemotherapeutic drugs, thereby downregulating the drug sensitivity [79]. In breast cancer, inhibiting integrin α2β1 can upregulate the expression of wild-type p53. At the same time, glioma cells can inhibit the expression of wild-type p53 by upregulating integrin α5 to enhance tumor chemotherapy resistance [80]. Recent studies have found that the integrin α5β1/AKT/PEA15/caspase8 signaling pathway in glioma can directly regulate the activity of p53. Integrins can also interact with p53 through the downstream protein kinase focal adhesion kinase (FAK), thus inhibiting its activity [81]. In PC, integrin β1 is also found to mediate mutant p53-driven cancer invasion, which needs the facilitation of a filopodia-inducing motor protein, Myosin-X (Myo10). Experiments using a Myo10 mutant without the integrin-binding domain revealed that the ability of Myo10 to transport integrin β1 to the filopodia tip is required for invasion. The introduction of mutant p53 promoted Myo10 expression in a mouse PC model, whereas suppression of endogenous mutant p53 attenuated Myo10 levels and cell invasion. These results suggest that cell components that contribute to plasma-membrane protrusions, such as integrin β1, may serve as specialized metastatic engines for mutant p53-driven PC [82]. It is believed that activation of p53 function is a vital strategy to intervene in tumor progression [83]. The studies mentioned above imply that inhibiting the activity of integrins and their
4.3. Integrin β1 and Cell Apoptosis

Regulation of the normal cell cycle via interaction of integrins with ECM is crucial in promoting embryonic development and maintaining tissue homeostasis. The imbalance of this interaction and the resulting inactivation of the downstream PI3K/AKT, MEK/ERK, FAK, NF-κB, and ILK signaling pathways could trigger abnormal cell apoptosis [84]. During tumor metastasis, due to disengagement from the interaction with ECM, cancer cells exhibit an enhanced ability to resist apoptosis by reprogramming the expression of integrins [85]. In hepatoma cells, upregulation of miR-26a can inhibit the expression of integrin α5 and promote tumor apoptosis [86]. It has been reported that melanoma cells express the matrix metalloproteinase inhibitor 1 (TIMP1) to resist apoptosis by forming complexes with CD63 and integrin β1 [87]. In breast cancer, upregulation of integrin α6β1 can decrease the expression of non-receptor tyrosine kinase FER in the cytoplasm, thereby impairing the ability to resist apoptosis [88]. In addition, vacuolar–ATPase inhibitors have been shown to regulate the anti-apoptotic ability of various tumor cells by reducing the activity of integrin β1 [51], and the zinc finger transcription factor ZNF304 can enhance the resistance to cell apoptosis by regulating integrin β1 transcription [89,90]. In PC, integrin β1 is also reported to be involved in apoptosis. Notably, numerous materials have been identified to regulate this process. For example, methylseleninic acid can induce entosis by cell detachment through downregulation of Cdc42 and integrin β1, and fucoxanthinol (FxOH) suppresses apoptosis of PANC-1 cells by upregulating the expression of integrin β1, FAK, paxillin, FYN, AKT, and PPARγ [91,92].

4.4. Integrin β1 and Angiogenesis

The involvement of integrins in regulating angiogenesis under various conditions has been extensively investigated. In tumor therapy, αvβ3/β5 is the first group of integrins identified to have the function of promoting the growth of new tumor vessels, and its functional antagonist cilengitide is also the first anti-tumor angiogenesis drug used in clinical research [93]. Unfortunately, cilengitide failed to improve overall survival in a multicenter, randomized, controlled phase 3 study in glioma [94]. Subsequent studies suggest that the antitumor effect of cilengitide is closely related to the time and dose of administration, and different conditions may lead to opposite results [95]. α5β1 is another integrin that promotes tumor angiogenesis [70,96]. Studies on the molecular mechanism behind the β1 subunit regulating angiogenesis found that angiopoietin-2, Arf6, VE-cadherin, and MAP4K4 were involved in activating the β1 signaling pathway, thereby regulating the subsequent angiogenesis process [97–100]. Integrins can accelerate the growth of new blood vessels and enhance the resistance to anti-angiogenic drugs. Bevacizumab, a commonly used anti-tumor angiogenesis drug, has shown promising effects in treating various tumors [101]. In clinical practice, however, drug resistance emerged during the treatment of glioma with Bevacizumab. Studies have detected that the expression of integrin α5β1 and its ligand fibronectin in drug-resistant tumor cells is significantly increased, while interfering with the expression of β1 can restore the sensitivity of tumor cells to Bevacizumab and improve the therapeutic efficacy [102,103]. While anti-angiogenic drugs have not been applied in the treatment of PC, research on the engagement of integrin β1 in PC angiogenesis has also achieved progress. Studies reveal that the loss of integrin β1 binding to fibulin-5 (Fbln5) can inhibit tumor angiogenesis in endothelial cells by increasing the level of ROS, suggesting that blocking Fbln5 function or interaction between Fbln5 and integrin β1 could be an effective anti-tumor strategy, alone or in combination with other therapies [104].

downstream signaling pathways will provide a new approach to activating p53 and will become a novel research orientation in the field of tumor therapy.
4.5. Integrin β1 and Metastasis

Early metastasis is a hallmark of PC pathology. The entire metastatic process involves the following distinct steps: EMT, invasion, intravasation (from primary tumor sites to enter blood vessels or lymphatic vessels), extravasation (from circulation to distant metastasis sites), and colonization to form secondary malignant tumor [105,106]. During this process, the roles of integrin β1 go all from the beginning to the end [107,108]. By activating integrin β1, the HGF/c-Met signaling pathway can promote the EMT transformation of gastric cancer [109–112]. Sheng et al. found that EGF simultaneously induced EMT and activated the integrin β1/EGFR-ERK/MAPK signaling pathway in three PC cell lines. This pathway could be further regulated by Calreticulin (CRT). Immunofluorescence showed that CRT was co-stained with pEGFR1173, fibronectin, and integrin β1 in PC cells, and overexpressing CRT reverted the change in EMT-related proteins induced by EGF. These results indicate a crucial function of the integrin β1/EGFR-ERK/MAPK axis signaling pathway in the EMT of PC [113].

Early studies show that tumor cells degrade and remodel the ECM by regulating the expression of matrix metalloproteinases (MMPs) through integrin signaling, thereby promoting invasion [114,115]. In PC, such effects of integrin β1 are executed by MMP-2. Eukaryotic elongation factor-2 kinase (eEF-2K) is an atypical kinase that is highly upregulated in PC cells. Researchers found that downregulation of eEF-2K impaired the invasion of PC cells and significantly decreased the expression of tissue transglutaminase (TG2), a multifunctional enzyme implicated in the regulation of cell attachment, motility, and survival. These alterations were associated with reductions in β1 integrin/uPAR/MMP-2 expressions and suppression in Src activity. Meanwhile, the induction of EMT biomarkers was also compromised by this axis, as demonstrated by the alterations of the zinc finger transcription factors, ZEB1/Snail, and the tight junction protein claudins. Therefore, the β1 integrin/Src/uPAR/MMP-2 signaling pathway represents a novel potential therapeutic target for PC invasion and EMT [116].

Apart from facilitating invasion, matrix proteolysis is also engaged in tumor cell intravasation. The behind mechanism involves the production of growth factors and cytokines, which stimulate neo-angiogenesis [117]. After circulation in the blood, the next critical step for tumor cells is extravasation. Integrins expressed on both cancer cells and endothelial cells have implications in extravasation. It has been illustrated that endothelial integrin α5 can bind to neuropilin 2 (NRP2), a multi-functional non-kinase receptor for diverse growth factors expressed on cancer cells, mediating extravasation. In the mouse PC model, by interacting with integrin α5 on the endothelial cell, the PC cell can bind to the endothelium and accomplish vascular extravasation [118]. Regarding colonization after extravasation, research shows that blockage of activated integrin α5β1 inhibits both lung and bone colonization of breast cancer cells [119]. Although similar experiments in PC have not been reported, these studies demonstrate that integrins, especially integrin β1, are in close relationship with tumor metastasis, and, therefore might become a critical target for suppressing PC progression.

4.6. Integrin β1 and Tumor Microenvironment (TME)

As cancer develops, it causes alterations in the surrounding tissue to create a favorable tumor microenvironment (TME) for its successful growth. It mainly includes ECM, surrounding blood vessels, immune cells, fibroblasts, and various signaling molecules [120]. It is currently believed that integrins specifically expressed on the cell surface and the corresponding composition of ECM in the tumor microenvironment are the key factors that determine the distant metastasis of tumor cells [121]. For example, liver metastasis of colon cancer depends on whether tumor cells express integrins α2β1 and α5β1 that facilitate cell survival in the liver microenvironment [122]. Similarly, cancer cells metastasize to the bone via the expression of integrins αvβ3, α2β1, and α4β1 that bind to specific ligands in the bone ECM [123]. Pancreatic stellate cells (PSCs) are the most abundant stromal cell types in PC. They are a major source of tumor-associated fibroblasts (CAFs) that can be
activated through growth factors secreted by cancer cells. Collagen type V, expressed by PSCs, can affect the malignant phenotype of various PC cell lines, and stable downregulation of collagen type V in PSCs could reduce metastasis in a PC mouse model. This was further shown to be mediated by β1 integrin signaling, since pharmacological and antibody-mediated inhibition of β1 integrin signaling abolished collagen type V-induced effects on PC cells [124]. Integrins β1 are also expressed in CAFs. Studies on non-small cell lung cancer demonstrate that knocking out integrin α1β1 in CAFs can interrupt the interaction between tumor cells and CAF and ultimately block the distant metastasis of lung cancer [125]. In PC, galectin 3 (GAL3), a β-galactoside-specific lectin, contributes to PC development by stimulating IL8 transcription through integrin β1 on PSCs, further activating NF-κB through integrin-linked kinase (ILK). Thus, inhibiting integrin β1 expression on PSCs can potentially block PC growth [126]. Regarding immune response, it has been illustrated that upregulation of integrin αv expression can lower the sensitivity of tumor cells to immune attack caused by chemotherapeutic drugs [127, 128]. Additionally, through the synergistic effect of integrin α5β1 and the extracellular matrix tenasin C, tumor cells can avoid the infiltration and attack of the surrounding immune cells [128]. In vivo experiments found that upregulation of the expression of integrin α4β1 can stimulate the activation and infiltration of T lymphocytes in the tumor tissues, thereby restraining tumor growth [129]. Recent research has found that normal immune cells can promote tumor metastasis in a specific environment, and it is speculated that the mechanism could be that tumor cells might enhance the invasion and metastasis activities by interacting with integrin αMβ2 contained in exosomes secreted by immune cells [130]. Research on the regulation of PC tumor immunity by integrin β1 is still lacking, but this may hopefully become a future direction for further investigation.

4.7. Integrin β1 and CSCs

Recently, a subpopulation of cells with self-renewal and differentiation abilities, termed CSCs, has been described and is assumed to be the driver for malignant characteristics by engaging in the processes of tumor growth, metastasis, and drug resistance [131–133]. CSCs are often identified with an expression of stemness markers including CD24, CD44, Nanog, CD133, Sox2, Sox9, essential specific antigen (ESA), and Kruppel-like factor 4 (KLF4) [134–136]. Integrins have been illustrated to play a pivotal part in cancer initiation, progression, and differentiation, indicating their contribution to CSC properties in diverse human cancers, including PC [137]. Barnawi and his colleagues analyzed the expression profiles of β1 integrin in 530 breast cancer patients and reported a correlation between β1 integrin and fascin expression; further research demonstrated that fascin facilitated the abilities of adhesion, self-renewal, and chemoresistance in breast cancer cells through β1 integrin [138, 139]. In mice lacking β1-integrin function, complete inhibition of tumorigenesis was observed; in the mammary gland, tissue-specific loss of function of β1 integrin can effectively abrogate the generation and proliferation of CD24hiCD29loCD61hi cancer cells [140, 141]. Studies in squamous cell carcinoma reveal that α6hiβ1hi cells can initiate secondary tumors while those with α6loβ1lo expression cannot, providing evidence for integrin β1-mediated CSC properties [142]. In PC, researchers isolated CD24hiCD44+ cells from the PANC-1 cell line and proved increased invasion ability of these cells compared to CD24loCD44+ cells. Using lectin microarray and nano LC-MS/MS, they identified upregulated integrin β1 expression in CD24hiCD44+ stem-like cells [143]. Mechanistically, PC cells can activate CAFs and increase collagen synthesis, which further leads to enhanced PC self-renewal and migration, as well as increased frequency of CSCs through FAK activation. Inhibition of the integrin β1/FAK signaling in PC cells significantly blocked the impact of CAFs on clonogenic growth [144]. Another research work reports that pancreatic CSCs express elevated aldehyde dehydrogenase (ALDH), which are associated with metastatic property [145]. β1 integrin–FAK expression was enriched in these ALDH+ CSCs, and further FAK inhibition abrogates clonogenic PC growth in vitro and in vivo [146]. These findings demonstrate that β1 integrin enhances CSC properties and promotes tumor initiation, self-renewal, and
metastasis through FAK signaling. Therefore, targeting integrin β1 may potentially be applied as a potent approach for PC treatment to restrain CSC survival and aggressiveness.

4.8. Integrin β1 and Therapy

Surgical resection remains the preferential approach for PC in the early stages. In contrast, for advanced PC, radiotherapy and chemotherapeutic agents, including gemcitabine (Gem), nab-paclitaxel, 5-fluorouracil (5-FU), and FOLFIRINOX, are generally recommended as adjuvant options. Despite the great progress made in these strategies, the overall survival (OS) of PC patients is still unsatisfactory due to the generation of chemo- or radioresistance [147]. Apart from actions on tumor pathogenesis and progression, increasing numbers of data show that integrins also play important roles in resistance to treatment. Patients with higher levels of integrin β1 tend to be more resistant to chemotherapy and display a worse clinical outcome [148]. We will discuss various factors that are more or less involved in integrin β1-mediated therapeutic resistance.

The extensive desmoplastic reaction is a prominent pathological feature of PC and shapes a physical barrier for drug delivery. Under the control of growth factors secreted by PC cells, PSCs can be activated and are responsible for dense ECM deposition, which, in turn, regulates resistance to standard therapies through interaction with tumor cells based on various adhesion molecules, with integrins being the largest family [149–151]. A previous study demonstrated that under treatment with 5-FU and Gem, PC cells cultured on collagen V-coated plates exhibit significantly increased survival rates compared to the controls, which can be reversed by inhibiting the integrin β1 signaling pathway [124]. In 95% of PC cases, activating mutations in the KRAS oncogene are detected, but clinical agents that directly target mutant KRAS are, so far, not available. Nevertheless, inhibition of downstream effectors, including the MAPK signaling pathway and PI3K signaling pathway, has received increasing attention these days [152,153]. In a 3D culture model of PC, MEK inhibition induced apoptotic lumen formation, a single-layered cluster with the cells at the periphery of the cluster displaying resistance to MEK inhibition while the cells in the interior layers undergo apoptosis. Following administration of the integrin β1 neutralizing antibody, the cells in the matrigel matrix were scattering, and survival in the context of MEK inhibition significantly decreased [154]. Taken together, these data suggest the pivotal role of integrin β1 signaling in the treatment resistance of PC induced by interaction with ECM.

Cumulative evidence supports that integrins can also contribute to drug resistance by interacting membrane proteins other than ECM. For instance, integrin β1 and Caveolin-1(Cav-1), a cell membrane component protein at Caveolae, co-participate in cell motility, invasion, and chemoresistance in lung cancer as well as PC [155,156]. Notably, the radiosensitivity of PC cells was enhanced, and integrin β1 expression was significantly reduced after Cav-1 silencing [157,158]. Additionally, integrins can also crosstalk with GFR and transactivate RTK signaling, even in the absence of growth factor ligand, which indicates that integrin signaling has a relationship with acquired resistance to molecularly targeted agents such as Cetuximab, which was discussed earlier in this manuscript [150] [159].

Regarding the crosstalk mechanism between EGFR and integrins, FAK plays a prominent role in many similar signaling pathways that integrins share with EGFR. At the molecular level, FAK is phosphorylated and activated at distinct domains interacting with various cytoplasmic proteins such as paxillin, Src, PI3K, Grb2, and many others, initiating several downstream signaling pathways [160–162]. It is worth noting that through the assembly of FAK-Src-p130Cas complex, the JNK signaling pathway can be activated, leading to negative regulation of equilibrative nucleoside transporter 1 (ENT1) [162,163]. The ENT1 is well known for mediating gemcitabine intracellular transport and resistance in humans and has, therefore, been proposed as an attractive potential prognostic biomarker for gemcitabine response in PC [164–166]. A recent study showed that increased α3 and β1 expression and subsequent activation of integrin α3β1 signaling via JNK inhibit the expression of ENT1, which reduced gemcitabine uptake and accumulation into PC cells [167].
Apart from drugs, integrin β1 has also been reported to be involved in cell-adhesion dependent radioresistance via direct contact between PSCs and PC cells. Mantoni et al. demonstrated, for the first time, that PSCs promote radioprotection of PC cells under a direct coculture condition rather than a conditioned medium from PSCs, which is attributed to the integrin β1-FAK signaling activation [168]. A further study, conducted by Mohamed et al., also confirmed the role of FAK signaling in improving PSCs-dependent radiosensitivity of cancer cells. The results showed that the FAK–tyrosine kinase inhibitor, VS-4718, can sensitize PC cells for radiation only in the presence of ECM-producing PSCs. The combination of VS-4718 and radiotherapy significantly reduced the growth of tumor aggregates in the 3D multicellular tumor model [169]. These effects may be attributed to impaired DNA repair, arrested cell cycle, and enhanced PC stem cell function [144,169,170].

A schematic diagram of the roles of integrin β1 in the malignant behaviors of PC is shown in Figure 2.

**Figure 2.** Roles of integrin β1 in the malignant behaviors of PC. Integrin β1 is involved in every step of PC progression and is responsible for regulating malignant cell behaviors such as sustained proliferation, apoptosis resistance, angiogenesis, and migration, as well as CSC property. Integrin β1 also promotes PC metastasis, including EMT, invasion, intravasation, circulation, extravasation, and colonization. In the tumor microenvironment, integrin β1 has been implicated in extensive desmoplastic reaction and regulates the expression of MMPs, the release of GF, and the activation and infiltration of lymphocytes. In addition, integrin β1 also plays an important role in the acquisition of treatment resistance.
5. Clinical Significance of Integrin β1 in PC

Thus far, since no other effective screening techniques or biomarkers other than CA19-9 have been identified for PC, most patients (80–85%) are already in an advanced stage when diagnosed, and the survival rate remains low [171]. Therefore, the need to explore more reliable biomarkers with adequate sensitivity and specificity for the diagnosis and prognosis of PC is urgent. Numerous studies have demonstrated the abnormal expression of integrin β1, which is closely related to the progression, metastasis, and prognosis of PC. Here, we present a list of recent studies researching the feasibility of integrin β1 as a diagnostic and prognostic biomarker in PC (Table 2).

Recently, a bioinformatic analysis showed that the expression of integrin β1 is remarkably increased in PC tissue samples compared with normal pancreas specimens based on TCGA and Oncomine databases. The ROC curve revealed that integrin β1 functions as a crucial indicator for PC diagnosis, with an AUC value of 0.86. Furthermore, the assessment of integrin β1 expression in different stages of PC demonstrated that patients in the late stage present higher expression of integrin β1 than those in the early stage [172]. However, upregulation of integrins is also reported in non-tumor benign diseases of the pancreas. A study by Chen et al. illustrated that integrin β1 was also overexpressed in chronic pancreatitis tissue, but to a lower degree compared with PC [173]. These findings suggest that integrin β1 might not be suitable as an early diagnostic indicator, but is of particular significance for assessing the progression and prognosis of PC.

Despite the relatively high clinical value of tissue-expressed integrin β1, the specimens mentioned above were obtained surgically, making it inconvenient and unacceptable for early screening and detection of PC. Therefore, methods through specimens, which can be easily accessed, are much more worth expecting. In 30 preoperative PC patients, the expression of integrin β1 mRNA in peripheral blood mononuclear cells (PBMCs) was significantly higher than that in healthy individuals. Moreover, the mRNA level of integrin β1 was significantly associated with the clinical stage and liver metastasis of PC [174]. The significant correlation between integrin β1 protein expression in PBMC and clinical features in PC patients was further confirmed by subsequent analysis [175].
Table 2. Overview of the clinical significance of integrin β1 in pancreatic cancer.

| No | Year | Detection Method | Source | Expression | No. of Patients | Lymphatic Invasion | Distance Metastasis | TNM Stage | AUC a | Survival | Prognostic Marker | Reference PMID |
|----|------|------------------|--------|------------|-----------------|-------------------|--------------------|-----------|-------|----------|------------------|----------------|
| 1  | 2012 | PCR              | PBMC b | up         | 37              | +                 | +                  | +         |       |          |                  | 22382453       |
| 2  | 2012 | PCR              | PBMC   | up         | 30              | +                 | +                  | +         |       |          |                  | 22695923       |
| 3  | 2013 | PCR, ELISA     | PBMC, plasma | up | 54          | +                | +                  | +         |       | DFS c  | +                | 24004467       |
| 4  | 2016 | IHC             | tissue | up         | 63              |                   |                     |           |       | OS d, DFS | +                | 27289231       |
| 5  | 2017 | IHC             | tissue | up         | 68              |                   | +                  |           |       | OS      | +                | 29072694       |
| 6  | 2018 | IHC             | tissue | up         | 30              |                   |                     |           |       | OS, DFS | +                | 29988949       |
| 7  | 2019 | IHC             | tissue | up         | 102             |                   |                     |           |       | + (combined with PODXL/BCL7B) | 31166991 |
| 8  | 2020 | IHC             | tissue | up         | 93              |                   |                     |           |       | OS, DFS | +                | 31711924       |
| 9  | 2021 | public database | tissue | up         | 178             |                   |                     |           | 0.8635 | OS, DFS | +                | 33591944       |

a. AUC: area under the curve; b. PBMC: peripheral blood mononuclear cell; c. DFS: disease-free survival; d. OS: overall survival. “+” means that integrin β1 could be used as a prognostic biomarker in PC.
In addition to diagnosis, there is ample evidence assessing integrin β1 regarding the prognosis of PC patients. In a previous study, integrin β1 expression in 68 cases of PC tissues was investigated by immunohistochemistry (IHC), verifying the positive integrin β1 staining in the cytoplasm and cytomembrane of PC cells and describing a positive association between integrin β1 overexpression and UICC stage of PC patients. Importantly, Kaplan–Meier survival analysis proved that overexpression of integrin β1 contributed to the poor prognosis of these PC patients [113]. Another study included 54 PC patients who received no other treatment, such as chemotherapy, radiation therapy, or immunotherapy, before and after cryosurgery and analyzed the dynamic change of integrin β1 expression in PBMC after cryosurgery. They found that integrin β1 expression decreased dramatically in the later stage, especially three months after treatment. However, the mRNA and protein levels of integrin β1 increased ten days after cryosurgery, which may be attributed to the destruction of tumor cells in the initial stage after cryosurgery. Moreover, the results indicate that the expression of integrin β1 mRNA and protein was correlated with disease-free survival (DFS) and overall survival (OS) in PC, and they could function as independent prognostic factors for OS but not for DFS. These data suggest that integrin β1 expression in the blood may become a promising biomarker for evaluating the outcome of cryosurgery in PC patients [175,176]. Additionally, a retrospective analysis of 63 primary PC patients who received adjuvant gemcitabine chemotherapy after pancreatectomy shows that OS and DFS were shorter in patients with high integrin β1 staining than in those with low integrin β1 staining [148]. Similar results were observed in another recent study. In this study, the researchers examined the prognostic significance in 102 PC patients who received adjuvant chemotherapy or chemoradiation therapy after resection. They found that patients with overexpression of integrin β1 had significantly shorter postoperative survival time than those with low integrin β1 levels. Notably, the combination of integrin β1 with PODXL/BCL7B more accurately predicted the postoperative outcomes of PC patients, which were superior to the UICC TNM staging system [177]. In conclusion, these findings indicate that integrin β1 is an independent predictor of worse postoperative survival of PC and could be used as a reliable biomarker for forecasting the response to adjuvant therapies prior to their initiation.

6. Future Expectations

Apart from apoptosis, autophagy, necroptosis, and pyroptosis, ferroptosis is a new type of programmed cell death that is iron-dependent. The primary mechanism of ferroptosis is that, under the action of ferrous iron or ester oxygenase, unsaturated fatty acids highly expressed on the cell membrane are catalyzed for lipid peroxidation, thereby inducing cell death. In addition, decreased expression of the antioxidant system, including glutathione and glutathione peroxidase 4 (GPX4), is another manifestation of ferroptosis [178,179]. Previous studies report that the α6β4 integrin saves adherent epithelial and carcinoma cells from ferroptosis induced by erastin and ECM detachment [180]. The mechanism behind this involves suppressing proferroptotic membrane lipids through ACSL4, which is an enzyme that promotes ferroptosis by enriching membranes with long polyunsaturated fatty acids. Further experiments unveiled that this suppression is achieved by α6β4-mediated activation of Src and STAT3 [181]. This link between α6β4 and ferroptosis implicates potential strategies for cancer therapy. Thus far, treatment targeting α6β4-mediated ferroptosis has not been reported, but integrins could serve as a guide for ferroptosis-based drugs. For example, Xu et al. report the facile construction of a multifunctional theranostic nanoplatform based on doxorubicin (DOX)-loaded tannic acid (TA)-iron (Fe) networks (for short, TAF) coated with fibronectin for combination tumor chemotherapeutic therapy. With the help of fibronectin, this platform can specifically target tumor cells with high expression of αvβ3 integrin [182]. Similar drugs have also been developed for ferroptosis therapy of orthotopic brain tumors [183]. Research on integrin β1-associated ferroptosis in PC is not available to date. Still, considering the function of integrin β1 in cell attachment,
we infer that integrin β1 might play a role in ferroptosis, and related therapies could be further expected.

Apart from existing on cell membranes of cancer cells and stromal cells, integrins are also contained in exosomes. Exosomes are late endosome-derived small extracellular vesicles (EVs) that assist intercellular communication under various conditions [184]. As a carrier for multiple molecules, including nucleic acid fragments, proteins, and lipids, exosomes play a vital role in cancer progression [185, 186]. Several studies have verified the role of exosomal integrins in PC. For example, integrin β4 increases PC growth, migration, and invasion by regulating plectin inclusion in the exosomes; exosomal integrin αvβ5 supports liver metastasis by interacting with fibronectin-rich ECM [187, 188]. Another study found that loss of protein kinase D1 contributed to metastasis of pancreatic tumors to the lung in mice by increasing the release of EVs, which showed upregulated loading of integrin α6β4. However, the specific role of α6β4 here still awaits further exploration [189]. Although Casari et al. demonstrate that integrin β1 was equally expressed in malignant vs. non-malignant exosomes, it does not mean exosomal integrin β1 is not involved in PC progression, and more profound research is needed to clarify the possible association [190].

Thus far, numerous preclinical models have indicated that integrin β1 is of potential therapeutic benefit in PC alone or in combination with the standard of care. Nevertheless, clinical studies have not received encouraging results. Even for the whole integrin family, most integrin-targeting strategies failed to reach the market, mainly due to a lack of therapeutic efficacy and safety. Volociximab is a chimeric monoclonal antibody against integrin α5β1 and can prevent neovascularization and suppress tumor growth and metastasis in preclinical studies [191]. Unfortunately, a multicenter, two-cohort phase II trial illustrated that a combination treatment of gemcitabine with volociximab did not enhance treatment efficacy over monotherapy in patients with metastatic PC. Moreover, volociximab has thus far failed to show benefit for patients with melanoma, ovarian cancer, or non-small cell lung cancer [192, 193]. In addition to volociximab, several other monoclonal antibodies against integrin β1, such as OS2966 and P5, have been reported in clinical trials. Specifically, OS2966, a first-in-class, humanized, and de-immunized monoclonal antibody anti-β1 integrin which is tested in patients with high-grade glioma (HGG) [194], and P5, a pan-β1 murine monoclonal antibody which is claimed to act at α5β1 predominantly, are reported in PH3 trials for NSCLC [195]. However, no clinical trials regarding these anti-pan-β1 antibodies have been tested in PC, and whether they deserve further testing in PC is an open question. In regards to other integrin β1 inhibitors, such as ATN-161 and natalizumab, no clinical trials have been carried out in PC, though they have already failed to yield satisfying outcomes in other solid tumors [196]. Obviously, it is challenging to translate the preclinical data on integrin β1 into clinically efficacious drugs considering the complex and wide-ranging roles of integrin β1 in tumors.

Several factors have complicated the development of integrin-based therapeutics for cancer [197, 198]. First, many integrins exhibit an overlapping ligand-binding spectrum with other integrin heterodimers. Another integrin binding the same ligand can compensate for the effect of blocking one integrin with a single agent. This functional redundancy and compensation between different integrins could explain the good tolerance but limited therapeutic effects of these integrin inhibitors [191, 192]. Second, the knowledge of integrins' different roles in distinct disease models and stages is far from being understood. Patients enrolled in the clinical trials are always in advanced disease stages and often have extensive treatment histories. The integrin expression patterns may have changed and become complicated with a mix of primary and metastatic lesions. For example, while depletion of integrin β1 suppresses the progression of several tumors, it could enhance tumorigenesis and proliferation in prostate cancer [196]. Likewise, Moritz et al. present a dual role of integrin α2β1 in breast cancer, that inhibiting α2β1 expression may be beneficial to limit the expansion of primary tumors but could be harmful once tumors establish in bone [199]. Besides, it has been reported that some antagonists can, to some extent, be agonists under certain conditions and induce the receptor to extend and adapt to a high-affinity ligand-binding
state, which may paradoxically enhance angiogenesis and tumor growth [200–202]. Third, most integrin-based therapeutics in clinical trials, including antibodies or peptides, typically block integrin function by occupying the ligand-binding site. During conformational changes, the bent form corresponding to a low-affinity conformer can also engage ligands without inducing activation signals [203]. Moreover, compared to allosteric inhibitors, which can lead to rapid dissolution of the integrin–ligand complex, integrin antagonists are unable to disrupt pre-existing integrin–ligand interactions, which may be one of the possible explanations for the lack of efficacy in the clinical trials [204]. Thus, allosteric inhibitors could also be powerful adjuvants to existing integrin therapies. Fourth, the lack of suitable preclinical models which can accurately represent human biology is a general problem in drug testing. It is challenging to correlate preclinical models with the actual clinical situation of patients with advanced and metastatic disease. Fifth, safety and tolerability are critical factors that cannot be ignored in the translation of preclinical data. Given the crucial role of integrin β1 in maintaining the integrity of the skin and upper gastrointestinal tracts, targeting the entire β family may not be achievable due to the interference with normal physiological processes and unacceptable toxicity [150]. Furthermore, it is worth noting that integrin β1 is a significant carrier of N-glycans, which are thought to play crucial roles in many biological functions [205]. N-glycans are complex forms of post-translational modifications (PTMs) and exhibit different structures in a space and time-dependent manner. Thus, the structural heterogeneity of N-glycans on integrin β1 among different individual patients may also be a non-negligible factor that affects the inhibition efficiency of β1, which leads to the failure of integrin β1-targeted therapeutics in clinical trials. In short, all the above mechanisms may lead to the failure of integrating integrin-targeting treatment in PC. Therefore, a deeper exploration of the efficacy and feasibility of targeted drugs needs to be conducted to overcome these obstacles in the future.

Since integrin-targeted inhibitors experienced setbacks in clinical trials, peptides targeting integrins are being proposed for their usefulness in drug delivery and non-invasive tumor imaging [206,207]. A functionalized liposome decorated with the integrin α5β1 binding peptide PR_b has been engineered for the local and sustained delivery of GEM and paclitaxel to PC, leading to a significant reduction in tumor growth [208]. This local delivery platform of integrin-targeted peptides on the surface of liposomal-like vesicles offers the advantage of achieving maximum therapeutic efficacy while minimizing toxic side effects to normal tissues. Additionally, an increasing number of molecules targeting integrins have been developed and investigated for molecular imaging in different cancers [209,210]. A 68Ga-radiolabeled peptide tracer targeting integrin αvβ6 has shown the ability of diagnostic imaging and post-surgery tumor relapse monitoring by performing preliminary clinical PET imaging on PC patients [211]. As for integrin β1, Li et al. developed a 68Ga-radiolabeled peptide tracer targeting the integrin α3β1 and unveiled significant radioactivity accumulation in PC cells and high tumor uptake in a xenografts mouse model [212]. With molecular imaging becoming an indispensable tool for noninvasive assessment of biological processes at the cellular or molecular level, we believe that integrin β1-based tracers will achieve high sensitivity and specificity when detecting lesions commonly missed by other technologies.

PTMs on integrins have been extensively studied in tumors due to their implications in tumor pathogenesis. Integrins can be regulated by many types of PTMs, including phosphorylation, glycosylation, ubiquitination, nitrosylation, and acetylation [213]. During these PTMs, glycosylation has been relatively well studied. Although integrin-mediated adhesion is based on the binding of α and β subunits to a defined peptide sequence, the strength of this binding and hetero-dimer formation can be modulated by various factors, including the status of N-glycosylation of integrin [214]. For example, integrin α5β1 contains 26 potential N-linked glycosylation sites (14 in the α subunit and 12 in the β subunit); previous studies from our group clearly showed that N-glycosylation on the β-propeller domain of the α5 [215] and/or the I-like domain of the β1 subunit [216]
is essential for α5β1 expression on the cell surface. Moreover, remodeling of N-glycans on the integrin regulates its biological functions, including cell adhesion, migration, and proliferation [217–224]. In PC, Kuo et al. demonstrated that O-glycans on integrin β1 are modified by C1GALT1 and can regulate cell-ECM adhesion, which is associated with decreased tyrosine phosphorylation of FAK at Y397 in PC cells. Additionally, C1GALT1 also modifies O-glycans on α integrins, especially the αV and α5 subunits, and promotes PC cell invasiveness through the integrin–FAK signaling [225]. It is worth mentioning that deficiency of α1,6-Fucosyltransferase (FUT8), a sole enzyme responsible for catalyzing core fucosylation, inhibited cell migration and proliferation in both MIA PaCa-2 and PANC-1 cells, which may arise through the fucosylation on β1 integrin [226], suggesting FUT8 may be a potential therapeutic target for PDAC. Further studies are needed to focus on the role N-glycosylation of integrin β1 and its related glycosyltransferases during PC progression. Apart from glycosylation, phosphorylation, ubiquitination, nitrosylation, and acetylation are common PTM forms. In addition to other PTMs, tyrosine 792 in the membrane-proximal NPXY motif of the β integrin is selectively de-phosphorylated by density-enhanced phosphatase-1 (DEP-1), which further triggers integrin activation via talin recruitment and interferes with EGFR signaling [227]. Such roles of integrin β1 phosphorylation in PC have not been reported. Still, these findings suggest that strategies aimed to alter the PTM processes of integrin β1 are a promising approach to control PC progression.

7. Conclusions

Integrin β1, as the most common β subunit of the integrin family, has been confirmed to play a vital role in tumor initiation and progression and is responsible for regulating cell behaviors such as survival, proliferation, apoptosis, invasion, and migration differentiation, as well as CSC property. In this review, the examples given here highlight the intricate involvement of integrin β1 in every step of PC progression, from primary tumor formation to metastasis, indicating integrin β1 as an appealing target for the development of PC therapies. Although many preclinical efforts showed promising data, integrin β1-targeting PC therapies are few and often unsuccessful in clinical trials. These clinical failures reflect a tremendous challenge in translating the preclinical research on integrin β1 into clinically efficacious drugs. Further in-depth understanding of the molecular mechanisms regulating the heterogeneity and redundancies of integrin β1 functions will become the theoretical basis and guidance for developing appropriate clinical pharmacodynamic biomarkers to measure target engagement and proposing an alternative approach targeting integrin β1 in other cells contained in the TME. Additionally, nascent and developing strategies exploring integrin β1-based approaches as targets for the delivery of existing anticancer drugs and noninvasive tumor imaging will become a new research direction in the field of PC diagnosis and therapy.

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References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics. 2021. CA Cancer J. Clin. 2021, 71, 7–33. [CrossRef]
2. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin. 2021, 71, 209–249. [CrossRef] [PubMed]
3. Ryan, D.P.; Hong, T.S.; Bardeesy, N. Pancreatic adenocarcinoma. N. Engl. J. Med. 2014, 371, 2140–2141. [CrossRef] [PubMed]
4. Neoptolemos, J.P.; Kleeff, J.; Michl, P.; Costello, E.; Greenhal, W.; Palmer, D.H. Therapeutic developments in pancreatic cancer: Current and future perspectives. Nat. Rev. Gastroenterol. Hepatol. 2018, 15, 333–348. [CrossRef] [PubMed]

5. Vasen, H.; Ibrahim, I.; Ponce, C.G.; Slater, E.P.; Matthäi, E.; Carrato, A.; Earl, J.; Robbers, K.; van Mil, A.M.; Potjer, T.; et al. Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers. J. Clin. Oncol. 2016, 34, 2010–2019. [CrossRef]

6. Conroy, T.; Bachet, J.B.; Ayav, A.; Huguet, F.; Lambert, A.; Caramella, C.; Maréchal, R.; Van Laethem, J.L.; Ducrœux, M. Current standards and new innovative approaches for treatment of pancreatic cancer. Eur. J. Cancer 2016, 57, 10–22. [CrossRef]

7. Tempero, M.A. NCCN Guidelines Updates: Pancreatic Cancer. J. Natl. Compr. Canc. Netw. 2019, 17, 603–605. [CrossRef]

8. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. Cell 2011, 144, 646–674. [CrossRef]

9. Zienert, E.; Eke, I.; Aust, D.; Cordes, N. LIM-only protein FHL2 critically determines survival and radioresistance of pancreatic cancer cells. Cancer Lett. 2015, 354, 17–24. [CrossRef] [PubMed]

10. Kato, S.; Van Laethem, J.L.; Ducreux, M. Current and future perspectives. Nat. Rev. Gastroenterol. Hepatol. 2018, 15, 646–674. [CrossRef] [PubMed]

11. Incio, J.; Suboj, P.; Chin, S.M.; Vardam-Kaur, T.; Liu, H.; Hato, T.; Babykutty, S.; Chen, I.; Deshpande, V.; Jain, R.K.; et al. Metformin Reduces Desmoplasia in Pancreatic Cancer by Reprogramming Stellate Cells and Tumor-Associated Macrophages. PLoS ONE 2015, 10, e0141392. [CrossRef] [PubMed]

12. Jülich, D.; Cobb, G.; Melo, A.M.; McMillen, P.; Lawton, A.K.; Mochrie, S.G.; Rhoades, E.; Holley, S.A. Cross-Scale Integrin Regulation Organizes ECM and Tissue Topology. Dev. Cell 2015, 34, 33–44. [CrossRef]

13. Son, S.; Moroney, G.J.; Butler, P.J. β(1)-Integrin-Mediated Adhesion Is Lipid-Bilayer Dependent. Biophys. J. 2017, 113, 1080–1092. [CrossRef]

14. Barczyk, M.; Carracedo, S.; Gullberg, D. Integrins. Cell Tissue Res. 2010, 339, 269–280. [CrossRef]

15. Colombo, M.; Bianchi, A. Cell chemistry for the synthesis of RGD-containing integrin ligands. Int. J. Mol. Sci. 2019, 20, 1161. [CrossRef]

16. Shibue, T.; Brooks, M.W.; Inan, M.F.; Reinhardt, F.; Weinberg, R.A. The outgrowth of micrometastases is enabled by the formation of filopodium-like protrusions. Cancer Discov. 2012, 2, 706–721. [CrossRef]

17. Jin, S.; Lee, W.C.; Aust, D.; Pilarsky, C.; Cordes, N. β8 Integrin Mediates Pancreatic Cancer Cell Radiochroemoresistance. Mol. Cancer Res. 2019, 17, 2126–2138. [CrossRef]

18. Desgrosellier, J.S.; Lesparrer, J.; Seguin, L.; Gozzo, M.; Kato, S.; Franovic, A.; Yebra, M.; Mielgo, A.; Lowy, A.M.; Husain, H.; et al. An integrin β3-KRAS-RalB complex drives tumour stemness and resistance to EGFR inhibition. Nat. Cell Biol. 2014, 16, 457–468. [CrossRef] [PubMed]

19. Seguin, L.; Kato, S.; Franovic, A.; Camargo, M.F.; Lasperance, J.; Elliott, K.C.; Yebra, M.; Mielgo, A.; Lowy, A.M.; Husain, H.; et al. An integrin β3-KRAS-RalB complex drives tumour stemness and resistance to EGFR inhibition. Nat. Cell Biol. 2014, 16, 457–468. [CrossRef] [PubMed]

20. Desgrosellier, J.S.; Lesparrer, J.; Seguin, L.; Gozzo, M.; Kato, S.; Franovic, A.; Yebra, M.; Shattil, S.J.; Cheresu, D.A. Integrin avb3 drives slug activation and stemness in the pregnant and neoplastic mammary gland. Dev. Cell 2014, 30, 295–308. [CrossRef]

21. Shibe, T.; Brooks, M.W.; Iwan, M.F.; Reinhardt, F.; Weinberg, R.A. The outgrowth of micrometastases is enabled by the formation of filopodium-like protrusions. Cancer Discov. 2012, 2, 706–721. [CrossRef] [PubMed]

22. Jin, S.; Lee, W.C.; Aust, D.; Pilarsky, C.; Cordes, N. β8 Integrin Mediates Pancreatic Cancer Cell Radiochroemoresistance. Mol. Cancer Res. 2019, 17, 2126–2138. [CrossRef]

23. Desgrosellier, J.S.; Lesparrer, J.; Seguin, L.; Gozzo, M.; Kato, S.; Franovic, A.; Yebra, M.; Shattil, S.J.; Chereau, D.A. Integrin avb3 drives slug activation and stemness in the pregnant and neoplastic mammary gland. Dev. Cell 2014, 30, 295–308. [CrossRef]

24. Shibue, T.; Brooks, M.W.; Iwan, M.F.; Reinhardt, F.; Weinberg, R.A. The outgrowth of micrometastases is enabled by the formation of filopodium-like protrusions. Cancer Discov. 2012, 2, 706–721. [CrossRef] [PubMed]

25. Jin, S.; Lee, W.C.; Aust, D.; Pilarsky, C.; Cordes, N. β8 Integrin Mediates Pancreatic Cancer Cell Radiochroemoresistance. Mol. Cancer Res. 2019, 17, 2126–2138. [CrossRef]

26. Desgrosellier, J.S.; Lesparrer, J.; Seguin, L.; Gozzo, M.; Kato, S.; Franovic, A.; Yebra, M.; Shattil, S.J.; Chereau, D.A. Integrin avb3 drives slug activation and stemness in the pregnant and neoplastic mammary gland. Dev. Cell 2014, 30, 295–308. [CrossRef] [PubMed]

27. Shibue, T.; Brooks, M.W.; Iwan, M.F.; Reinhardt, F.; Weinberg, R.A. The outgrowth of micrometastases is enabled by the formation of filopodium-like protrusions. Cancer Discov. 2012, 2, 706–721. [CrossRef] [PubMed]

28. Jin, S.; Lee, W.C.; Aust, D.; Pilarsky, C.; Cordes, N. β8 Integrin Mediates Pancreatic Cancer Cell Radiochroemoresistance. Mol. Cancer Res. 2019, 17, 2126–2138. [CrossRef]

29. Desgrosellier, J.S.; Lesparrer, J.; Seguin, L.; Gozzo, M.; Kato, S.; Franovic, A.; Yebra, M.; Shattil, S.J.; Chereau, D.A. Integrin avb3 drives slug activation and stemness in the pregnant and neoplastic mammary gland. Dev. Cell 2014, 30, 295–308. [CrossRef] [PubMed]

30. Shibue, T.; Brooks, M.W.; Iwan, M.F.; Reinhardt, F.; Weinberg, R.A. The outgrowth of micrometastases is enabled by the formation of filopodium-like protrusions. Cancer Discov. 2012, 2, 706–721. [CrossRef] [PubMed]

31. Hamidi, H.; Ivaska, J. Every step of the way: Integrins in cancer progression and metastasis. Nat. Rev. Cancer 2018, 18, 533–548. [CrossRef] [PubMed]
32. Huveneers, S.; Danen, E.H. Adhesion signaling—Crosstalk between integrins, Src and Rho. J. Cell Sci. 2009, 122, 1059–1069. [CrossRef] [PubMed]
33. Chodniewicz, D.; Klemke, R.L. Regulation of integrin-mediated cellular responses through assembly of a CAS/Crk scaffold. Biochim. Biophys. Acta 2004, 1692, 63–76. [CrossRef]
34. Deakin, N.O.; Turner, C.E. Paxillin comes of age. J. Cell Sci. 2008, 121, 2435-2444. [CrossRef] [PubMed]
35. ten Klooster, J.P.; Jaffer, Z.M.; Chernoff, J.; Hordijk, P.L. Targeting and activation of Rac1 are mediated by the exchange factor beta-Pix. J. Cell Biol. 2006, 172, 759–769. [CrossRef] [PubMed]
36. Guilluy, C.; Swaminathan, V.; Garcia-Mata, R.; O’Brien, E.T.; Superfine, R.; Burridge, K. The Rho GEFs LARG and GEF-H1 regulate the mechanical response to force on integrins. Nat. Cell Biol. 2011, 13, 722–727. [CrossRef] [PubMed]
37. Moser, M.; Legate, K.R.; Zent, R.; Fassler, R. The tail of integrins, talin, and kindlins. Science 2009, 324, 895–899. [CrossRef] [PubMed]
38. Xu, Z.; Isaij, T.; Fukuda, T.; Wang, Y.; Gu, J. O-GlcNAcylation regulates integrin-mediated cell adhesion and migration via formation of focal adhesion complexes. J. Biol. Chem. 2019, 294, 3117–3124. [CrossRef] [PubMed]
39. Sun, Z.; Costell, M.; Fassler, R. Integrin activation by talin, kindlin and mechanical forces. Nat. Cell Biol. 2019, 21, 25–31. [CrossRef] [PubMed]
40. Lu, J.; Zhou, S.; Siech, M.; Habisch, H.; Seufferlein, T.; Bachem, M.G. Pancreatic stellate cells promote hapto-migration of cancer cells through collagen I-mediated signalling pathway. Br. J. Cancer 2014, 110, 409–420. [CrossRef] [PubMed]
41. Friedland, J.C.; Lee, M.H.; Boettiger, D. Mechanically activated integrin switch controls alpha5beta1 function. Science 2009, 323, 642–644. [CrossRef] [PubMed]
42. Moore, S.W.; Roca-Cusachs, P.; Sheetz, M.P. Stretchy proteins on stretchy substrates: The important elements of integrin-mediated rigidity sensing. Dev. Cell 2010, 19, 194–206. [CrossRef] [PubMed]
43. Kirmse, R.; Otto, H.; Ludwig, T. Interdependency of cell adhesion, force generation and extracellular proteolysis in matrix remodeling. J. Cell Sci. 2011, 124, 1857–1866. [CrossRef] [PubMed]
44. Malik, R.; Lelkes, P.I.; Cukierman, E. Biomechanical and biochemical remodeling of stromal extracellular matrix in cancer. Trends Biotechnol. 2015, 33, 230–236. [CrossRef] [PubMed]
45. Zeltz, C.; Alam, J.; Liu, H.; Erusappan, P.M.; Hoschuetzky, H.; Molven, A.; Parajuli, H.; Cukierman, E.; Costea, D.E.; Lu, N.; et al. α11β1 Integrin Is Induced in a Subset of Cancer-Associated Fibroblasts in Desmoplastic Tumor Stroma and Mediates In Vitro Cell Migration. Cancers 2019, 11, 765. [CrossRef] [PubMed]
46. Marcoux, N.; Vuori, K. EGFR receptor mediates adhesion-dependent activation of the Rac GTPase: A role for phosphatidylinositol 3-kinase and Vav2. Oncogene 2003, 22, 6100–6106. [CrossRef] [PubMed]
47. Takada, Y.; Takada, Y.K.; Fujita, M. Crosstalk between insulin-like growth factor (IGF) receptor and integrins through direct integrin binding to IGF1. Cytokine Growth Factor Rev. 2017, 34, 67–72. [CrossRef] [PubMed]
48. Sarker, F.A.; Prior, V.G.; Bax, S.; O’Neill, G.M. Forcing a growth factor response—Tissue-stiffness modulation of integrin signaling and crosstalk with growth factor receptors. J. Cell Sci. 2020, 133, jsc242461. [CrossRef] [PubMed]
49. Daou, D.T.; Anez-Bustillos, L.; Adam, R.M.; Puder, M.; Bielenberg, D.R. Heparin-Binding Epidermal Growth Factor-Like Growth Factor as a Critical Mediator of Tissue Repair and Regeneration. Am. J. Pathol. 2018, 188, 2446–2456. [CrossRef]
50. Malenica, I.; Adam, J.; Corgnac, S.; Mezquita, L.; Auclin, E.; Damei, I.; Grynszpan, L.; Gros, G.; de Montpreville, V.; Planchard, D.; et al. Integrin-α(V)-mediated activation of TGF-β regulates anti-tumour CD8 T cell immunity and response to PD-1 blockade. Nat. Commun. 2021, 12, 5209. [CrossRef] [PubMed]
51. Shi, M.; Zhu, J.; Wang, R.; Chen, X.; Mi, L.; Walz, T.; Springer, T.A. Latent TGF-β structure and activation. Nature 2011, 474, 343–349. [CrossRef] [PubMed]
52. Kemper, M.; Schiecke, A.; Maar, H.; Nikulin, S.; Poloznikov, A.; Galatenko, V.; Tachez, M.; Gebauer, F.; Lange, T.; Riecken, M.J.; Wiche, G. Molecular architecture and function of the hemidesmosome. Cell Tissue Res. 2015, 360, 363–378. [CrossRef] [PubMed]
53. Carley, E.; Stewart, R.M.; Ziemen, A.; Jalilian, I.; King, D.E.; Zubek, A.; Lin, S.; Horsley, V.; King, M.C. The LINC complex transmits integrin-dependent tension to the nuclear lamina and represses epidermal differentiation. eLife 2021, 10, e58541. [CrossRef] [PubMed]
54. Ren, D.; Zhao, J.; Sun, Y.; Li, D.; Meng, Z.; Wang, B.; Fan, P.; Liu, Z.; Jin, X.; Wu, H. Overexpressed ITGA2 promotes malignant tumor aggression by up-regulating PD-L1 expression through the activation of the STAT3 signaling pathway. J. Exp. Clin. Cancer Res. 2019, 38, 485. [CrossRef] [PubMed]
55. Aksorn, N.; Chanvorachote, P. Integrin as a Molecular Target for Anti-cancer Approaches in Lung Cancer. Anticancer Res. 2019, 39, 541–548. [CrossRef] [PubMed]
56. Justo, B.L.; Jasiulionis, M.G. Characteristics of TIMP1, CD63, and β1-Integrin and the Functional Impact of Their Interaction in Cancer. Int. J. Mol. Sci. 2021, 22, 9319. [CrossRef] [PubMed]
59. Pellinen, T.; Blom, S.; Sánchez, S.; Valimäki, K.; Mpindi, J.P.; Azegrouz, H.; Strippoli, R.; Nieto, R.; Vittón, M.; Palacios, I.; et al. ITGB1-dependent upregulation of Caveolin-1 switches TGFβ signalling from tumour-suppressive to oncogenic in prostate cancer. *Sci. Rep.* **2018**, *8*, 2338. [CrossRef]

60. Wang, K.; Zhu, X.; Mei, D.; Ding, Z. Caveolin-1 contributes to anoikis resistance in human gastric cancer SGC-7901 cells via regulating Src-dependent EGFR-ITGB1 signaling. *J. Biochem. Mol. Toxicol.* **2018**, *32*, e22202. [CrossRef]

61. Zhang, L.; Zhang, T.; Deng, Z.; Sun, L. MicroRNA-3653 inhibits the growth and metastasis of hepatocellular carcinoma by inhibiting ITGB1. *Oncol. Rep.* **2019**, *41*, 1669–1677. [CrossRef] [PubMed]

62. Seguin, L.; Desgrousliere, J.S.; Weis, S.M.; Cheres, D.A. Integrins and cancer: Regulators of cancer stemness, metastasis, and drug resistance. *Trends Cell Biol.* **2015**, *25*, 234–240. [CrossRef] [PubMed]

63. Najmeh, S.; Cools-Lartigue, J.; Rayes, R.F.; Gowing, S.; Vourtzoumis, P.; Bourdeau, F.; Giannias, B.; Berube, J.; Rousseau, S.; Ferri, L.E.; et al. Neutrophil extracellular traps sequester circulating tumor cells via β1-integrin mediated interactions. *Int. J. Cancer* **2017**, *140*, 2321–2330. [CrossRef] [PubMed]

64. Kim, J.; Fukuto, H.S.; Brown, D.A.; Bliska, J.B.; London, E. Effects of host cell sterol composition upon internalization of Yersinia pseudotuberculosis and clustered β1 integrin. *J. Biol. Chem.* **2018**, *293*, 1466–1479. [CrossRef]

65. Kawahara, R.; Niwa, Y.; Simizu, S. Integrin β1 is an essential factor in vasulogenic mimicry of human cancer cells. *Cancer Sci.* **2018**, *109*, 2490–2496. [CrossRef]

66. Beatty, B.T.; Sharma, V.P.; Bravo-Cordero, J.J.; Simpson, M.A.; Eddy, R.J.; Koleske, A.J.; Condeelis, J. β1 integrin regulates Arg to promote invadopodial maturation and matrix degradation. *Mol. Biol. Cell* **2013**, *24*, 1661–1675. [CrossRef]

67. Moreno-Layseca, P.; Streuli, C.H. Signalling pathways linking integrins with cell cycle progression. *Matrix Biol.* **2014**, *34*, 144–153. [CrossRef] [PubMed]

68. Mohan, S.; Heitzer, E.; Ulz, P.; Lafer, I.; Lax, S.; Auer, M.; Pichler, M.; Gerger, A.; Eisner, F.; Hoefer, G.; et al. Changes in colorectal carcinoma genomes under anti-EGFR therapy identified by whole-genome plasma DNA sequencing. *PloS Genet.* **2014**, *10*, e1004271. [CrossRef] [PubMed]

69. Rao, T.C.; Ma, V.P.; Blanchard, A.; Urner, T.M.; Grandhi, S.; Salaita, K.; Mattheys, A.L. EGFR activation attenuates the mechanical threshold for integrin tension and focal adhesion formation. *J. Cell Sci.* **2020**, *133*, jsc238840. [CrossRef]

70. Vial, D.; McKeown-Longo, P.J. Epidermal growth factor (EGF) regulates α5β1 integrin activation state in human cancer cell lines through the p90RSK-dependent phosphorylation of filamin A. *J. Biol. Chem.* **2012**, *287*, 40371–40380. [CrossRef]

71. Morozovich, G.E.; Kozlova, N.I.; Preobrazhenskaya, M.E.; Berman, A.E. Integrin α5β1-dependent upregulation of Caveolin-1 switches TGFβ signalling from tumour-suppressive to oncogenic in prostate cancer cells. *Sci. Rep.* **2018**, *8*, 2338. [CrossRef]

72. Petrak, M.; Lajtos, T.; Friedländer, E.; Klekner, A.; Pintye, E.; Feuerstein, B.G.; Szöllosi, J.; Vereb, G. Molecular interactions of ErbB1 (EGFR) and integrin-β1 in astrocytoma frozen sections predict clinical outcome and correlate with Akt-mediated in vitro radioresistance. *Neuro Oncol.* **2013**, *15*, 1027–1040. [CrossRef] [PubMed]

73. Kim, K.H.; Chen, C.C.; Alpini, G.; Lau, L.F. CCN1 induces hepatic ductular reaction through integrin

74. Wang, K.; Zhu, X.; Mei, D.; Ding, Z. Caveolin-1 contributes to anoikis resistance in human gastric cancer SGC-7901 cells via regulating Src-dependent EGFR-ITGB1 signaling. *J. Biochem. Mol. Toxicol.* **2018**, *32*, e22202. [CrossRef]

75. Zhang, L.; Zhang, T.; Deng, Z.; Sun, L. MicroRNA-3653 inhibits the growth and metastasis of hepatocellular carcinoma by inhibiting ITGB1. *Oncol. Rep.* **2019**, *41*, 1669–1677. [CrossRef] [PubMed]

76. Seguin, L.; Desgrousliere, J.S.; Weis, S.M.; Cheres, D.A. Integrins and cancer: Regulators of cancer stemness, metastasis, and drug resistance. *Trends Cell Biol.* **2015**, *25*, 234–240. [CrossRef] [PubMed]

77. Lee, J.G.; Ahn, J.H.; Jin Kim, T.; Ho Lee, J.; Choi, J.H. Mutant p53 promotes ovarian cancer cell adhesion to mesothelial cells via integrin β1 and Akt signals. *Sci. Rep.* **2015**, *5*, 12642. [CrossRef]

78. Savar, A.; Acin, S.; Gonzalez, C.L.; El-Sawy, T.; Mejia, O.; Li, Z.; Esmaeili, B.; Lacy-Hulbert, A.; El-Naggar, A.K.; McCarty, J.H.; et al. Loss of epithelial p53 and integrin α5β1 integrin activation state in human cancer cell lines through the p90RSK-dependent phosphorylation of filamin A. *J. Biol. Chem.* **2012**, *287*, 40371–40380. [CrossRef]

79. Kim, Y.J.; Jung, K.; Baek, D.S.; Hong, S.S.; Kim, Y.S. Co-targeting of EGF receptor and neuropilin-1 overcomes cetuximab resistance in pancreatic ductal adenocarcinoma with integrin α5β1-dependent pro-survival signaling in epithelial carcinoma cells. Aging **2012**, *4*, 368–374. [CrossRef] [PubMed]

80. Martin, S.; Janouskova, H.; Dontenwill, M. Integrins and p53 pathways in glioblastoma resistance to temozolomide. *Cell Death Differ.* **2016**, *23*, 640–653. [CrossRef] [PubMed]

81. Arjonen, A.; Kaukonen, R.; Mattila, E.; Rouhi, P.; Högnäs, G.; Sihto, H.; Miller, B.W.; Morton, J.P.; Bucher, E.; Taimen, P.; et al. Mutant p53-associated myosin-X upregulation promotes breast cancer invasion and metastasis. *J. Clin. Investig.* **2014**, *124*, 1069–1082. [CrossRef] [PubMed]

82. Selivanova, G. Wild type p53 reactivation: From lab bench to clinic. *FEBS Lett.* **2014**, *588*, 2628–2638. [CrossRef] [PubMed]
84. Griffiths, G.S.; Grundl, M.; Leychenko, A.; Reiter, S.; Young-Robbins, S.S.; Sulzmaier, F.J.; Caliva, M.J.; Ramos, J.W.; Matter, M.L. Bit-1 mediates integrin-dependent cell survival through activation of the NFκB pathway. *J. Biol. Chem.* 2011, 286, 14713–14723. [CrossRef] [PubMed]

85. Buchheit, C.L.; Weigel, K.J.; Schafer, Z.T. Cancer cell survival during detachment from the ECM: Multiple barriers to tumour progression. *Nat. Rev. Cancer* 2014, 14, 632–641. [CrossRef]

86. Zhang, X.; Cheng, S.L.; Bian, K.; Wang, L.; Zhang, X.; Yan, B.; Jia, L.T.; Zhao, J.; Gammoh, N.; Yang, A.G.; et al. MicroRNA-26a promotes anoikis in human hepatocellular carcinoma cells by targeting alpha5 integrin. *Oncotarget* 2015, 6, 2277–2289. [CrossRef]

87. Toricelli, M.; Melo, F.H.; Peres, G.B.; Silva, D.C.; Jasiulionis, M.G. Timp1 interacts with beta-1 integrin and CD63 along melanoma gene and confers anoikis resistance by activating PI3-K signaling pathway independently of Akt phosphorylation. *Mol. Cancer* 2013, 12, 22. [CrossRef]

88. Ivanova, I.A.; Vermeulen, J.F.; Erkan, C.; Houthuijzen, J.M.; Saig, F.A.; Vlug, E.J.; van der Wall, E.; van Diest, P.J.; Vooijs, M.; Derksen, P.W. FER kinase promotes breast cancer metastasis by regulating α6- and β1-integrin-dependent cell adhesion and anoikis resistance. *Oncogene* 2013, 32, 5582–5592. [CrossRef]

89. Schempp, C.M.; von Schwarzenbach, K.; Schreiner, L.; Kubisch, R.; Müller, R.; Wagner, E.; Vollmar, A.M. V-ATPase inhibition regulates anoikis resistance and metastasis of cancer cells. *Mol. Cancer Ther.* 2014, 13, 926–937. [CrossRef]

90. Aslan, B.; Monroig, P.; Hsu, M.C.; Pena, G.A.; Rodriguez-Aguayo, C.; Gonzalez-Villasana, V.; Rupaimoole, R.; Nagaraja, A.S.; Mangala, S.; Han, H.D.; et al. The ZNF304-integrin axis protects against anoikis in cancer. *Nat. Commun.* 2015, 6, 7351. [CrossRef]

91. Khalkar, P.; Diaz-ArgeIich, N.; Antonio Palop, J.; Sammartin, C.; Fernandez, A.P. Novel Methylselenoesters Induce Programmed Cell Death via Entosis in Pancreatic Cancer Cells. *Int. J. Mol. Sci.* 2018, 19, 2849. [CrossRef] [PubMed]

92. Terasaki, M.; Takahashi, S.; Nishimura, R.; Kubota, A.; Kojima, H.; Ohta, T.; Hamada, J.; Kuramitsu, Y.; Maeda, H.; Miyashita, K.; et al. A Marine Carotenoid of Fucoxanthinol Accelerates the Growth of Human Pancreatic Cancer PANC-1 Cells. *Nutr. Cancer* 2022, 74, 357–371. [CrossRef] [PubMed]

93. Stupp, R.; Hegi, M.E.; Yin, B.; Goldbrunner, R.; Schlegel, U.; Clement, P.M.; Grabenbauer, G.G.; Ochsenbein, A.F.; Simon, M.; Dietrich, P.Y.; et al. Phase I/IIa study of cilengitide and temozolomide with concomitant radiotherapy followed by cilengitide and temozolomide maintenance therapy in patients with newly diagnosed glioblastoma. *J. Clin. Oncol.* 2010, 28, 2712–2718. [CrossRef] [PubMed]

94. Stupp, R.; Hegi, M.E.; Gorlia, T.; Erridge, S.C.; Perry, J.; Hong, Y.K.; Aldape, K.D.; Lhermitte, B.; Pietsch, T.; Grujicic, D.; et al. Beta1 integrins inhibit tumor growth by increasing the level of ROS. *Oncotarget* 2015, 6, 7328–7349. [CrossRef] [PubMed]

95. Eisele, G.; Wick, A.; Eisele, A.C.; Clément, P.M.; Tonn, J.; Tabatabai, G.; Ochsenbein, A.; Schlegel, U.; Neys, B.; Krex, D.; et al. Cilengitide treatment of newly diagnosed glioblastoma patients does not alter patterns of progression. *J. Neurooncol.* 2014, 117, 141–145. [CrossRef] [PubMed]

96. Janouskova, H.; Ray, A.M.; Noulet, F.; Lelong-Rebel, I.; Choulier, L.; Schaffner, F.; Lehmann, M.; Martin, S.; Teisinger, J.; Dontenwill, A. Beta-integrin: Critical path to antiangiogenic therapy resistance and beyond. *Cancer Res.* 2013, 73, 333–342. [CrossRef] [PubMed]

97. Hakanpaa, L.; Sipila, T.; Leppanen, V.M.; Gautam, P.; Nurmi, H.; Jacquemet, G.; Eklund, L.; Ivaska, J.; Alitalo, K.; Saharinen, P. Endothelial destabilization by angiopoietin-2 via integrin β1 activation. *Nat. Commun.* 2015, 6, 5962. [CrossRef] [PubMed]

98. Hongu, T.; Funakoshi, Y.; Fukuhara, S.; Suzuki, T.; Sakimoto, S.; Takakura, N.; Ema, M.; Takahashi, S.; Itoh, S.; Kato, M.; et al. Arf6 regulates tumour angiogenesis and growth through HGF-induced endothelial β1 integrin recycling. *Nat. Commun.* 2015, 6, 7925. [CrossRef] [PubMed]

99. Vitorino, P.; Yeung, S.; Crow, A.; Bakke, J.; Smyczek, T.; West, K.; McNamara, E.; Eastham-Anderson, J.; Gould, S.; Harris, S.F.; et al. MAP4K4 regulates integrin-FERM binding to control endothelial cell motility. *Nature* 2015, 519, 425–430. [CrossRef]

100. Yamamoto, H.; Ehling, M.; Kato, K.; Kanai, K.; van Lessen, M.; Frye, M.; Zeuschner, D.; Nakayama, M.; Vestweber, D.; Adams, R.H. Integrin β1 controls VE-cadherin localization and blood vessel stability. *Nat. Commun.* 2015, 6, 6429. [CrossRef]

101. Herrlinger, K.R.; Diculescu, M.; Fellermann, K.; Hartmann, H.; Howaldt, S.; Nikolov, R.; Petrov, A.; Reindl, W.; Otte, J.M.; Stoynov, S.; et al. Efficacy, safety and tolerability of vidofludum in patients with inflammatory bowel disease: The ENTRANCE study. *J. Crohns Colitis* 2013, 7, 636–643. [CrossRef] [PubMed]

102. Carbonell, W.S.; DeLay, M.; Jahangiri, A.; Park, C.C.; Aghi, M.K. β1 integrin targeting potentiates antiangiogenic therapy and inhibits the growth of bevacizumab-resistant glioblastoma. *Cancer Res.* 2013, 73, 3145–3154. [CrossRef] [PubMed]

103. Jahangiri, A.; Aghi, M.K.; Carbonell, W.S. β1 integrin: Critical path to antiangiogenic therapy resistance and beyond. *Cancer Res.* 2014, 74, 3–7. [CrossRef] [PubMed]

104. Schluterman, M.K.; Chapman, S.L.; Korpanty, G.; Ozumi, K.; Fukai, T.; Yanagisawa, H.; Breken, R.A. Loss of filamin-5 binding to beta1 integrins inhibits tumor growth by increasing the level of ROS. *Dis. Model. Mech.* 2010, 3, 333–342. [CrossRef]

105. Akhtar, M.; Haider, A.; Rashid, S.; Al-Nabat, A. Paget’s “Seed and Soil” Theory of Cancer Metastasis: An Idea Whose Time has Come. *Adv. Anat. Pathol.* 2019, 26, 69–74. [CrossRef] [PubMed]

106. Peinado, H.; Zhang, H.; Matei, I.R.; Costa-Silva, B.; Hoshino, A.; Rodrigues, G.; Psaila, B.; Kaplan, R.N.; Bromberg, J.F.; Kang, Y.; et al. Pre-metastatic niches: Organ-specific homes for metastases. *Nat. Rev. Cancer* 2017, 17, 302–317. [CrossRef]
107. Naci, D.; Vuori, K.; Aoudjit, F. Alpha2beta1 integrin in cancer development and chemoresistance. *Semin. Cancer Biol.* 2015, 35, 145–153. [CrossRef]

108. Eke, I.; Cordes, N. Focal adhesion signaling and therapy resistance in cancer. *Semin. Cancer Biol.* 2015, 31, 65–75. [CrossRef]

109. Zhou, P.; Erfani, S.; Liu, Z.; Jia, C.; Chen, Y.; Xu, B.; Deng, X.; Alfáro, J.E.; Chen, L.; Napier, D.; et al. CD151-α2β1 integrin complexes are prognostic markers of glioblastoma and cooperate with EGFR to drive tumor cell motility and invasion. *OncoTarget* 2015, 6, 29675–29693. [CrossRef]

110. Li, X.; Ishihara, S.; Yasuda, M.; Nishioka, T.; Mizutani, T.; Ishikawa, M.; Kawabata, K.; Shirato, H.; Haga, H. Lung cancer cells that survive ionizing radiation show increased integrin α2β1- and EGFR-dependent invasiveness. *PLoS ONE* 2013, 8, e70905. [CrossRef]

111. Williams, K.C.; Coppolino, M.G. SNARE-dependent interaction of Src, EGFR and β1 integrin regulates invadopodia formation and tumor cell invasion. *J. Cell Sci.* 2014, 127, 1712–1725. [CrossRef] [PubMed]

112. Mai, A.; Muharram, G.; Barrow-McGee, R.; Baghirov, H.; Rantala, J.; Kermorgant, S.; Ivaska, J. Distinct c-Met activation mechanisms induce cell rounding or invasion through pathways involving integrins, RhoA and HIP1. *J. Cell Sci.* 2014, 127, 1938–1954. [CrossRef] [PubMed]

113. Sheng, W.; Chen, C.; Dong, M.; Wang, G.; Zhou, J.; Song, H.; Li, Y.; Zhang, J.; Ding, S. Calreticulin promotes EGF-induced EMT in pancreatic cancer cells via Integrin/EGFR-ERK/MAPK signaling pathway. *Cell Death Dis.* 2017, 8, e3147. [CrossRef] [PubMed]

114. Borrirukwanit, K.; Pavasant, P.; Blick, T.; Lafleur, M.A.; Thompson, E.W. High threshold of β1 integrin inhibition required to block collagen I-induced membrane type-1 matrix metalloproteinase (MT1-MMP) activation of matrix metalloproteinase 2 (MMP-2). *Cancer Cell Int.* 2014, 14, 99. [CrossRef]

115. Dong, F.; Eibach, M.; Bartsch, J.W.; Dolga, A.M.; Schlomann, U.; Conrad, C.; Schieber, S.; Schilling, O.; Biniossek, M.L.; Culmsee, C.; et al. The metalloprotease-disintegrin ADAM8 contributes to temozolomide chemoresistance and enhanced invasiveness of human glioblastoma cells. *Neuro Oncol.* 2015, 17, 1474–1485. [CrossRef]

116. Ashour, A.A.; Gurbuz, N.; Alpay, S.N.; Abdel-Aziz, A.A.; Mansour, A.M.; Huo, L.; Ozpolat, B. Elongation factor-2 kinase regulates TG2/β1 integrin/Src/uPAR pathway and epithelial-mesenchymal transition mediating pancreatic cancer cells invasion. *J. Cell. Mol. Med.* 2014, 18, 2235–2251. [CrossRef] [PubMed]

117. Egeblad, M.; Rasch, M.G.; Weaver, V.M. Dynamic interplay between the collagen scaffold and tumor evolution. *Curr. Opin. Cell Biol.* 2010, 22, 697–706. [CrossRef]

118. Handa, A.; Tokunaga, T.; Tsuchida, T.; Lee, Y.H.; Kijima, H.; Yamazaki, H.; Ueyama, Y.; Fukuda, H.; Nakamura, M. Neuropilin-2 Signaling. *Cell Death Dis.* 2014, 5, 697–706. [CrossRef]

119. Yao, H.; Veine, D.M.; Livant, D.L. Therapeutic inhibition of breast cancer bone metastasis progression and lung colonization: Breaking the vicious cycle by targeting α5β1 integrin. *Breast Cancer Res. Treat.* 2016, 157, 489–501. [CrossRef]

120. Foster, D.S.; Jones, R.E.; Ransom, R.C.; Longaker, M.T.; Norton, J.A. The evolving relationship of wound healing and tumor stroma. *JCI Insight* 2018, 3, e99911. [CrossRef]

121. Grzesiak, J.J.; Tran Cao, H.S.; Burton, D.W.; Kaushal, S.; Vargas, F.; Clopton, P.; Snyder, C.S.; Deftos, L.J.; Hoffman, R.M.; Bouvet, M. Knockdown of the β(1) integrin subunit reduces primary tumor growth and inhibits pancreatic cancer metastasis. *Int. J. Cancer* 2011, 129, 2905–2915. [CrossRef] [PubMed]

122. Pelillo, C.; Bergamo, A.; Mollica, H.; Bestagno, M.; Sava, G. Colorectal Cancer Metastases Settle in the Hepatic Microenvironment Through α5β1 Integrin. *J. Cell. Biochem.* 2015, 116, 2385–2396. [CrossRef] [PubMed]

123. Esposito, M.; Kang, Y. Targeting tumor-stromal interactions in bone metastasis. *Pharmacol. Ther.* 2014, 141, 222–233. [CrossRef]

124. Berchtold, S.; Grünwald, B.; Krüger, A.; Reithmeier, A.; Hahl, T.; Cheng, T.; Feuchtinger, A.; Born, D.; Erkan, M.; Kleeff, J.; et al. Collagen type V promotes the malignant phenotype of pancreatic ductal adenocarcinoma. *Cancer Lett.* 2015, 356, 721–732. [CrossRef] [PubMed]

125. Navab, R.; Strumpf, D.; To, C.; Pasko, E.; Kim, K.S.; Park, C.J.; Hai, J.; Liu, J.; Jonkman, J.; Barczyk, M.; et al. Integrin α11β1 regulates cancer stromal stiffness and promotes tumorigenicity and metastasis in non-small cell lung cancer. *Oncoogene* 2016, 35, 1899–1908. [CrossRef]

126. Zhao, W.; Ajani, J.A.; Sushovan, G.; Ochi, N.; Hwang, R.; Hafley, M.; Johnson, R.L.; Bresalier, R.S.; Logsdon, C.D.; Zhang, Z.; et al. Galectin-3 Mediates Tumor Cell-Stroma Interactions by Activateing Pancreatic Stellate Cells to Produce Cytokines via Integrin Signaling. *Gastroenterology* 2018, 154, 1524–1537.e1526. [CrossRef]

127. Anikeeva, N.; Steblyanko, M.; Fayngerts, S.; Kopylova, N.; Marshall, D.J.; Powers, G.D.; Sato, T.; Campbell, K.S.; Sykulev, Y. Integrin receptors on tumor cells facilitate NK cell-mediated antibody-dependent cytotoxicity. *Eur. J. Immunol.* 2014, 44, 2331–2339. [CrossRef] [PubMed]

128. Jagiotti, E.; Caputo, S.; Mazzonei, S.; Brambillasca, C.S.; Parigi, S.M.; Griioni, M.; Piras, I.S.; Restuccia, U.; Calcinoatto, A.; Freschi, M.; et al. Tenascin-C Protects Cancer Stem-like Cells from Immune Surveillance by Arresting T-cell Activation. *Cancer Res.* 2015, 75, 2095–2108. [CrossRef] [PubMed]

129. Cantor, J.M.; Rose, D.M.; Slepak, M.; Ginsberg, M.H. Fine-tuning Tumor Immunity with Integrin Trans-regulation. *Cancer Immunol. Res.* 2015, 3, 661–667. [CrossRef] [PubMed]
130. Ma, J.; Cai, W.; Zhang, Y.; Huang, C.; Zhang, H.; Liu, J.; Tang, K.; Xu, P.; Katirai, F.; Zhang, J.; et al. Innate immune cell-derived microparticles facilitate hepatocarcinoma metastasis by transferring integrin αMβ2 to tumor cells. *J. Immunol.* 2013, 191, 3435–3461. [CrossRef]

131. Yadav, A.K.; Desai, N.S. Cancer Stem Cells: Acquisition, Characteristics, Therapeutic Implications, Targeting Strategies and Future Prospects. *Stem Cell Rev. Rep.* 2019, 15, 331–355. [CrossRef] [PubMed]

132. Islam, F.; Gopalan, V.; Lam, A.K. Identification of Cancer Stem Cells in Esophageal Adenocarcinoma. *Methods Mol. Biol.* 2018, 1756, 165–176. [CrossRef] [PubMed]

133. Huang, X.; Xiao, R.; Pan, S.; Yang, X.; Yuan, W.; Tu, Z.; Xu, M.; Zhu, Y.; Yin, Q.; Wu, Y.; et al. Uncovering the roles of long non-coding RNAs in cancer stem cells. *J. Hematol. Oncol.* 2017, 10, 62. [CrossRef]

134. Prasad, S.; Ramachandran, S.; Gupta, N.; Kaushik, I.; Srivastava, S.K. Cancer cells stemness: A doorstep to targeted therapy. *Biochim. Biophys. Acta Mol. Basis Dis.* 2020, 1866, 165424. [CrossRef]

135. Lahlou, H.; Sanguin-Gendreau, V.; Zuo, D.; Cardiff, R.D.; McLean, G.W.; Frame, M.C.; Muller, W.J. Mammary epithelial-specific disruption of the focal adhesion kinase blocks mammary tumor progression. *Proc. Natl. Acad. Sci. USA* 2007, 104, 20302–20307. [CrossRef]

136. Prasad, S.; Ramachandran, S.; Gupta, N.; Kaushik, I.; Srivastava, S.K. Cancer cells stemness: A doorstep to targeted therapy. *Biochim. Biophys. Acta Mol. Basis Dis.* 2020, 1866, 165424. [CrossRef]

137. Zheng, Y.; de la Cruz, C.C.; Sayles, L.C.; Alleyne-Chin, C.; Yaka, D.; Knaak, T.D.; Bigos, M.; Xu, Y.; Hoang, C.D.; Shrager, J.B.; et al. A rare population of CD24(+)/ITGB4(+)/Notch(+) cells drives tumor propagation in NSCLC and requires Notch3 for self-renewal. *Cancer Cell* 2013, 23, 59–74. [CrossRef]

138. Barnawi, R.; Al-Khalidi, S.; Majed Sleiman, G.; Sarkar, A.; Al-Dhifyan, A.; Al-Mohanna, F.; Ghebeh, H.; Al-Alwan, M. Fasillin is Critical for the Maintenance of Breast Cancer Stem Cell Pool Predominantly via the Activation of the Notch Self-Renewal Pathway. *Stem Cells* 2016, 34, 2799–2813. [CrossRef]

139. Jeong, B.Y.; Cho, K.H.; Jeong, K.; Park, Y.Y.; Kim, J.M.; Rha, S.Y.; Park, C.G.; Mills, G.B.; Cheong, J.H.; Lee, H.Y. Rab25 augments cancer cell invasiveness through a β1 integrin/EGFR/VEGF-A/Snail signaling axis and expression of fascin. *Exp. Mol. Med.* 2018, 50, e335. [CrossRef]

140. Lathia, J.; Liu, H.; Matei, D. The Clinical Impact of Cancer Stem Cells. *Cancers* 2019, 11, 743907. [CrossRef] [PubMed]

141. White, D.E.; Kurpios, N.A.; Zuo, D.; Hassell, J.A.; Blaess, S.; Mueller, U.; Muller, W.J. Targeted disruption of beta1-integrin in a transgenic mouse model of human breast cancer reveals an essential role in mammary tumor induction. *Cancer Cell* 2004, 6, 159–170. [CrossRef] [PubMed]

142. Schober, M.; Fuchs, E. Tumor-initiating stem cells of squamous cell carcinomas and their control by TGF-β and integrin/focal adhesion kinase (FAK) signaling. *Proc. Natl. Acad. Sci. USA* 2011, 108, 10544–10549. [CrossRef] [PubMed]

143. Zhu, J.; He, J.; Liu, Y.; Simeone, D.M.; Lubman, D.M. Identification of glycoprotein markers for pancreatic cancer CD24+CD44+ stem-like cells using nano-LC-MS/MS and tissue microarray. *J. Proteome Res.* 2012, 11, 2272–2281. [CrossRef] [PubMed]

144. Begum, A.; McMillan, R.H.; Chang, Y.T.; Penchev, V.R.; Rajeshkumar, N.V.; Maitra, A.; Goggins, M.G.; Eshelman, J.R.; Wolfgang, C.L.; Rasheed, Z.A.; et al. Direct Interactions With Cancer-Associated Fibroblasts Lead to Enhanced Pancreatic Cancer Stem Cell Function. *Pancetra* 2019, 40, 329–334. [CrossRef]

145. Rasheed, Z.A.; Yang, J.; Wang, Q.; Kowalski, J.; Freed, I.; Murter, C.; Hong, S.M.; Koorstra, J.B.; Rajeshkumar, N.V.; He, X.; et al. Prognostic significance of tumorigenic cells with mesenchymal features in pancreatic adenocarcinoma. *J. Natl. Cancer Inst.* 2010, 102, 340–351. [CrossRef]

146. Begum, A.; Ewachi, T.; Jung, C.; Huang, A.; Norberg, K.J.; Marchionni, L.; McMillan, R.; Penchev, V.; Rajeshkumar, N.V.; Maitra, A.; et al. The extracellular matrix and focal adhesion kinase signaling regulate cancer stem cell function in pancreatic ductal adenocarcinoma. *PLoS ONE* 2017, 12, e0180181. [CrossRef] [PubMed]

147. Carvalho, T.M.A.; Di Molfetta, D.; Greco, M.R.; Koltai, T.; Alfarouk, K.O.; Reshkin, S.J.; Cardone, R.A. Tumor Microenvironment Features and Chemoresistance in Pancreatic Ductal Adenocarcinoma: Insights into Targeting Physicochemical Barriers and Metabolism as Therapeutic Approaches. *Cancers* 2021, 13, 6135. [CrossRef]

148. Yang, D.; Shi, J.; Fu, H.; Wei, Z.; Xu, J.; Hu, Z.; Zhang, Y.; Yan, R.; Cai, Q. Integrinβ1 modulates tumour resistance to gemcitabine and serves as an independent prognostic factor in pancreatic adenocarcinomas. *Tumour Biol.* 2016, 37, 12153–12237. [CrossRef]

149. Cannon, A.; Thompson, C.; Hall, B.R.; Jain, M.; Kumar, S.; Batra, S.K. Desmoplasia in pancreatic ductal adenocarcinoma: Insight into pathological function and therapeutic potential. *Genes Cancer* 2018, 9, 78–86. [CrossRef]

150. Cooper, J.; Giancotti, F.G. Integrin Signalling in Cancer: Mechanotransduction, Stemness, Epithelial Plasticity, and Therapeutic Resistance. *Cancer Cell* 2019, 35, 347–367. [CrossRef] [PubMed]

151. Manoukian, P.; Bijlsma, M.; van Laarhoven, H. The Cellular Origins of Cancer-Associated Fibroblasts and Their Opposing Contributions to Pancreatic Cancer Growth. *Front. Cell Dev. Biol.* 2021, 9, 743907. [CrossRef] [PubMed]

152. Infante, J.R.; Somer, B.G.; Park, J.O.; Li, C.P.; Scheulen, M.E.; Kasubhai, S.M.; Oh, D.Y.; Liu, Y.; Redhu, S.; Steplewski, K.; et al. A Randomised, Double-blind, Placebo-controlled Trial of trametinib, an Oral MEK Inhibitor, in Combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas. *Eur. J. Cancer* 2014, 50, 2072–2081. [CrossRef] [PubMed]

153. Alagesan, B.; Contino, G.; Guimaraes, A.R.; Corcoran, R.B.; Deshpande, V.; Wojtkiewicz, G.R.; Hezel, A.F.; Wong, K.K.; Loda, M.; Weissleder, R.; et al. Combined MEK and PI3K inhibition in a mouse model of pancreatic cancer. *Clin. Cancer Res.* 2015, 21, 396–404. [CrossRef] [PubMed]
154. Brannon, A., 3rd; Drouillard, D.; Steele, N.; Schoettle, S.; Abel, E.V.; Crawford, H.C.; Pasca di Magliano, M. Beta 1 integrin signaling mediates pancreatic ductal adenocarcinoma resistance to MEK inhibition. Sci. Rep. 2020, 10, 11133. [CrossRef]

155. Petriéron, N.; Blummanahan, N.; Tungsskruthai, S.; Pinkhien, T.; Mauithed, A.; Sriturarak, B.; Chanhvorachote, P. Chrysotolobenzyl inhibition of lung cancer cell migration through Caveolin-1-dependent mediation of the integrin switch and the sensitization of lung cancer cells to cisplatin-mediated apoptosis. Phytomedicine 2019, 58, 152888. [CrossRef] [PubMed]

156. Whitney, N.P.; Lamb, A.C.; Louw, T.M.; Subramanian, A. Integrin-mediated mechanotransduction pathway of low-intensity ultrasonic irradiation. Strahlenther. Onkol. 2009, 185, 362–370. [CrossRef]

157. Hehlgans, S.; Eke, I.; Storch, K.; Haase, M.; Baretton, G.B.; Cordes, N. Caveolin-1 mediated radiosensitivity of 3D grown pancreatic cancer cells. Radiother. Oncol. 2009, 92, 362–370. [CrossRef]

158. Cordes, N.; Frick, S.; Brunner, T.B.; Pilsarsky, C.; Grützmann, R.; McKenna, W.G.; Bernhard, E.J. Human pancreatic tumor cells are sensitized to ionizing radiation by knockdown of caveolin-1. Oncogene 2007, 26, 6851–6862. [CrossRef]

159. Qian, Y.; Gong, Y.; Fan, Z.; Luo, G.; Huang, Q.; Deng, S.; Cheng, H.; Jin, K.; Ni, Q.; Yu, X.; et al. Molecular alterations and targeted therapy in pancreatic ductal adenocarcinoma. J. Hematol. Oncol. 2020, 13, 130. [CrossRef]

160. Whitney, N.P.; Lamb, A.C.; Louw, T.M.; Subramanian, A. Integrin-mediated mechanotransduction pathway of low-intensity continuous ultrasound in human chondrocytes. Ultrasound Med. Biol. 2012, 38, 1734–1743. [CrossRef]

161. Mushtag, U.; Bashir, M.; Nabi, S.; Khanday, F.A. Epidermal growth factor receptor and integrins mediate redox signaling through P63/65c and Rac1. Cytokine 2021, 146, 156526. [CrossRef] [PubMed]

162. Javadi, S.; Zhiani, M.; Mousavi, M.A.; Fathi, M. Crosstalk between Epidermal Growth Factor Receptors (EGFR) and integrins in pancreatic cancer. Mol. Biotechnol. 2019, 1, 3377. [CrossRef] [PubMed]

163. Leisewitz, A.V.; Zimmerman, E.I.; Huang, M.; Jones, S.Z.; Yang, J.; Graves, L.M. Regulation of ENT1 expression and ENT1-dependent nucleoside transport by c-Jun N-terminal kinase. Biochem. Biophys. Res. Commun. 2011, 404, 370–375. [CrossRef] [PubMed]

164. Binenbaum, Y.; Na’ara, S.; Gil, Z. Gemcitabine resistance in pancreatic ductal adenocarcinoma. Drug Resist. Updates 2015, 23, 55–68. [CrossRef] [PubMed]

165. Greenhalf, W.; Ghaneh, P.; Neoptolemos, J.P.; Palmer, D.H.; Cox, T.F.; Lamb, R.F.; Garner, E.; Campbell, F.; Mackey, J.R.; Costello, E.; et al. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. J. Natl. Cancer Inst. 2014, 106, djt347. [CrossRef]

166. Nordi, S.; Ansari, D.; Andersson, R. hENT1 expression is predictive of gemcitabine outcome in pancreatic cancer: A systematic review. World J. Gastroenterol. 2014, 20, 8482–8490. [CrossRef]

167. Liu, M.; Zhang, Y.; Yang, J.; Cui, X.; Zhou, Z.; Zhan, H.; Ding, K.; Tian, X.; Yang, Z.; Fung, K.A.; et al. ZIP4 Increases Expression of β1-integrin signaling and Inhibit Expression of the Gemcitabine Transporter ENT1 in Pancreatic Cancer Cells. Gastroenterology 2020, 158, 679–692.e671. [CrossRef]

168. Mantoni, T.S.; Lunardi, S.; Al-Assar, O.; Masamune, A.; Brunner, T.B. Pancreatic stellate cells radiosensitize pancreatic cancer cells through β1-integrin signaling. Cancer Res. 2011, 71, 3453–3458. [CrossRef]

169. Mohamed, A.A.; Thomsen, A.; Follo, M.; Zamboglou, C.; Brunsert, P.; Mostafa, H.; Amen, A.; Mekawy, M.; Grosu, A.L.; Brunner, T.B. FAK inhibition radiosensitizes pancreatic ductal adenocarcinoma cells in vitro. Strahlenther. Onkol. 2021, 197, 27–38. [CrossRef]

170. Al-Assar, O.; Demiciorglu, F.; Lunardi, S.; Gaspar-Carvalho, M.M.; McKenna, W.G.; Muschel, R.M.; Brunner, T.B. Contextual regulation of pancreatic cancer stem cell phenotype and radiosensitivity by pancreatic stellate cells. Radiother. Oncol. 2014, 111, 243–251. [CrossRef]

171. Conroy, T.; Hammel, P.; Hebbing, M.; Ben Abdelghani, M.; Wei, A.C.; Raoul, J.L.; Chone, L.; Francois, E.; Artru, P.; Biagi, J.J.; et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N. Engl. J. Med. 2013, 369, 1296–1305. [CrossRef]

172. Jie, Y.; Peng, W.; Li, Y.Y. Identification of novel candidate biomarkers for pancreatic adenocarcinoma based on TCGA cohort. Aging 2021, 13, 5698–5717. [CrossRef] [PubMed]

173. Chen, R.; Brentnall, T.A.; Pan, S.; Cooke, K.; Moyes, K.W.; Lane, Z.; Crispin, D.A.; Goodlett, D.R.; Aebbersold, R.; Brunner, M.P. Quantitative proteomics analysis reveals that proteins differentially expressed in chronic pancreatitis are also frequently involved in pancreatic cancer. Mol. Cell. Proteom. 2007, 6, 1331–1342. [CrossRef] [PubMed]

174. Zhou, G.; Chiu, D.; Qin, D.; Niu, L.; Cai, J.; He, L.; Huang, W.; Xu, K. Detection and clinical significance of CD44v6 and integrin-β1 in pancreatic cancer patients using a triplex real-time RT-PCR assay. Appl. Biochem. Biotechnol. 2012, 167, 2257–2268. [CrossRef]

175. Zhou, G.; Chiu, D.; Qin, D.; Niu, L.; Cai, J.; He, L.; Tan, D.; Xu, K. Expression of CD44v6 and integrin-β1 for the prognosis evaluation of pancreatic cancer patients after cryosurgery. Diagn. Pathol. 2013, 8, 146. [CrossRef]

176. Zhou, G.; Chiu, D.; Qin, D.; Niu, L.; Cai, J.; He, L.; Huang, W.; Xu, K. The efficacy evaluation of cryosurgery in pancreatic cancer patients with the expression of CD44v6, integrin-β1, CA199, and CEA. Mol. Biotechnol. 2012, 52, 59–67. [CrossRef] [PubMed]

177. Taniuchi, K.; Furihata, M.; Naganuma, S.; Sakaguchi, M.; Saibara, T. Overexpression of PODXL/ITGB1 and BCL7B/ITGB1 accurately predicts unfavorable prognosis compared to the TNM staging system in postoperative pancreatic cancer patients. PLoS ONE 2019, 14, e0217920. [CrossRef]
185. Plebanek, M.P.; Angeloni, N.L.; Vinokour, E.; Li, J.; Henkin, A.; Martinez-Marin, D.; Filleur, S.; Bhowmick, R.; Henkin, J.; Miller, S.D.; et al. Pre-metastatic cancer exosomes induce immune surveillance by patrolling monocytes at the metastatic niche. Nat. Commun. 2017, 8, 1319. [CrossRef] [PubMed]

186. Anderson, R.L.; Balasas, T.; Callaghan, J.; Coombes, R.C.; Evans, J.; Hall, J.A.; Kinrade, S.; Jones, D.; Jones, P.S.; Jones, R.; et al. A framework for the development of effective anti-metastatic agents. Nat. Rev. Clin. Oncol. 2019, 16, 185–204. [CrossRef]

187. Shin, S.J.; Smith, J.A.; Reznicek, G.A.; Pan, S.; Chen, R.; Brentnall, T.A.; Wiche, G.; Kelly, K.A. Unexpected gain of function for the scaffolding protein plectin due to mislocalization in pancreatic cancer. Proc. Natl. Acad. Sci. USA 2013, 110, 19414–19419. [CrossRef] [PubMed]

188. Hoshino, A.; Costa-Silva, B.; Shen, T.L.; Rodrigues, G.; Hashimoto, A.; Tesic Mark, M.; Molina, H.; Koohsaka, S.; Di Giannatale, A.; Voeller, J.; et al. Magnetic Nanoparticles for Ferroptosis Therapy of Orthotopic Brain Tumors. ACS Nano 2011, 5, 392–400. [CrossRef] [PubMed]

189. Li, J.; Cao, F.; Yin, H.L.; Huang, Z.J.; Lin, Z.T.; Mao, N.; Sun, B.; Wang, G. Ferroptosis: Past, present and future. Cell Death Dis. 2020, 11, 88. [CrossRef]

190. Casari, I.; Howard, J.A.; Robless, E.E.; Falasca, M. Exosomal integrins and their influence on pancreatic cancer progression and metastasis. Cancer Lett. 2021, 507, 124–134. [CrossRef] [PubMed]

191. Almokadem, S.; Belani, C.P. Volociximab in cancer. Expert Opin. Biol. Ther. 2012, 12, 251–257. [CrossRef] [PubMed]

192. Bell-McGuinn, K.M.; Matthews, C.M.; Ho, S.N.; Barve, M.; Gilbert, L.; Lengyel, E.; Palaparthi, R.; Gilder, K.; Vassos, A.; et al. Phase II, single-arm study of the anti-α5β1 integrin antibody volociximab as monotherapy in patients with platinum-resistant advanced epithelial ovarian or primary peritoneal cancer. Gynecol. Oncol. 2011, 121, 273–279. [CrossRef] [PubMed]

193. Besse, B.; Tsao, L.C.; Chao, D.T.; Fang, Y.; Soria, J.C.; Almokadem, S.; Belani, C.P. Phase Ib safety and pharmacokinetic study of volociximab, an anti-α5β1 integrin antibody, in combination with carboplatin and paclitaxel in advanced non-small-cell lung cancer. Ann. Oncol. 2013, 24, 90–96. [CrossRef] [PubMed]

194. Nwagwu, C.D.; Immidiseti, A.V.; Bukanowska, G.; Vogelbaum, M.A.; Carbonell, A.M. Convection-Enhanced Delivery of a First-in-Class Anti-β1 Integrin Antibody for the Treatment of High-Grade Glioma Utilizing Real-Time Imaging. Pharmaceutics 2020, 13, 40. [CrossRef]

195. Kim, M.Y.; Cho, W.D.; Hong, K.P.; Choi, J.; Hong, J.W.; Kim, S.; Moon, Y.R.; Son, S.M.; Lee, O.J.; Lee, H.C.; et al. Novel monoclonal antibody against beta 1 integrin enhances cisplatin efficacy in human lung adenocarcinoma cells. J. Biomed. Res. 2016, 30, 217–224. [CrossRef]

196. Cianfrocca, M.E.; Kimmel, K.A.; Gallo, J.; Cardoso, T.; Brown, M.M.; Hudes, G.; Lewis, N.; Weiner, L.; Lam, G.N.; Brown, S.C.; et al. Phase 1 trial of the antiangiogenic peptide ATN-161 (Ac-PHSCN-NH(2)), a beta integrin antagonist, in patients with solid tumours. Br. J. Cancer 2006, 94, 1621–1626. [CrossRef]

197. Parvani, J.G.; Galliher-Beckley, A.J.; Schemann, B.J.; Schemann, W.P. Targeted inactivation of β1 integrin induces β3 integrin switching, which drives breast cancer metastasis by TGF-β. Mol. Biol. Cell 2013, 24, 3439–3459. [CrossRef]

198. Pan, B.; Gao, J.; Liao, Q.; Zhao, Y. β1 and β3 integrins in breast, prostate and pancreatic cancer: A novel implication. Oncol. Lett. 2018, 15, 5412–5416. [CrossRef]

199. Moritz, M.N.O.; Merkel, A.R.; Feldman, E.G.; Selistre-de-Araujo, H.S.; Roihodes Sterling, J.A. Biphasic α2β1 Integrin Expression in Breast Cancer Metastasis to Bone. Int. J. Mol. Sci. 2021, 22, 6906. [CrossRef]

200. Reynolds, A.R.; Hart, I.R.; Watson, A.R.; Welti, J.C.; Silva, R.G.; Robinson, S.D.; Da Violante, G.; Gourlaouen, M.; Salih, M.; Jones, M.C.; et al. Stimulation of tumor growth and angiogenesis by low concentrations of RGD-mimetic integrin inhibitors. Nat. Med. 2009, 15, 392–400. [CrossRef] [PubMed]

201. Legler, D.F.; Wiedle, G.; Ross, F.P.; Imhof, B.A. Superactivation of integrin alphavbeta3 by low antagonist concentrations. J. Cell Sci. 2001, 114, 1545–1553. [CrossRef] [PubMed]
202. Tolomelli, A.; Galletti, P.; Baiula, M.; Giacomini, D. Can Integrin Agonists Have Cards to Play against Cancer? A Literature Survey of Small Molecules Integrin Activators. Cancers 2017, 9, 78. [CrossRef] [PubMed]

203. Zhu, J.; Zhu, J.; Negri, A.; Provadi, D.; Filizola, M.; Coller, B.S.; Springer, T.A. Closed headpiece of integrin αIIbβ3 and its complex with an αIIbβ3-specific antagonist that does not induce opening. Blood 2010, 116, 5050–5059. [CrossRef] [PubMed]

204. Mold, A.P.; Craig, S.E.; Byron, S.K.; Humphries, M.J.; Jowitt, T.A. Disruption of integrin-fibronectin complexes by allostERIC but not ligand-mimetic inhibitors. Biochem. J. 2014, 464, 301–313. [CrossRef]

205. Marsico, G.; Russo, L.; Quondamatteo, F.; Pandit, A. Glycosylation and Integrin Regulation in Cancer. Trends Cancer 2018, 4, 537–552. [CrossRef]

206. Fu, S.; Zhao, Y.; Sun, J.; Yang, T.; Zhi, D.; Zhang, E.; Zhong, F.; Zhen, Y.; Zhang, S.; Zhang, S. Integrin α(v)β(3)-targeted liposomal drug delivery system for enhanced lung cancer therapy. Colloids Surf. B Biointerfaces 2021, 201, 111623. [CrossRef]

207. Gao, J.; Wang, S.; Dong, X.; Wang, Z. RGD-expressed bacterial membrane-derived nanovesicles enhance cancer therapy via multiple tumorous targeting. Theranostics 2021, 11, 3301–3316. [CrossRef]

208. Shabana, A.M.; Kambhampati, S.P.; Hsia, R.C.; Kannan, R.M.; Kokkoli, E. Thermosensitive and biodegradable hydrogel encapsulating targeted nanoparticles for the sustained co-delivery of gemcitabine and paclitaxel to pancreatic cancer cells. Int. J. Pharm. 2021, 593, 120139. [CrossRef]

209. Zhang, J.; Niu, G.; Lang, L.; Li, F.; Fan, X.; Yan, X.; Yao, S.; Yan, W.; Huo, L.; Chen, L.; et al. Clinical Translation of a Dual Integrin avβ3- and Gastrin-Releasing Peptide Receptor-Targeting PET Radiotracer, 68Ga-BBN-RGD. J. Nucl. Med. 2017, 58, 228–234. [CrossRef]

210. Liu, S. Radiolabeled Cyclic RGD Peptide Bioconjugates as Radiotracers Targeting Multiple Integrins. Bioconjug. Chem. 2015, 26, 1413–1438. [CrossRef]

211. Feng, X.; Wang, Y.; Lu, D.; Xu, X.; Zhou, X.; Zhang, H.; Zhang, T.; Zhu, H.; Yang, Z.; Wang, F.; et al. Clinical Translation of a (68)Ga-Labeled Integrin α(v)β(6)-Targeting Cyclic Radiotracer for PET Imaging of Pancreatic Cancer. J. Nucl. Med. 2020, 61, 1461–1467. [CrossRef] [PubMed]

212. Li, H.; Yuan, L.; Long, Y.; Fang, H.; Li, M.; Liu, Q.; Xia, X.; Qin, C.; Zhang, Y.; Lan, X.; et al. Synthesis and Preclinical Evaluation of a (68)Ga-Radiolabeled Peptide Targeting Very Late Antigen-3 for PET Imaging of Pancreatic Cancer. Mol. Pharm. 2020, 17, 3000–3008. [CrossRef] [PubMed]

213. Hou, S.; Wang, J.; Li, W.; Hao, X.; Hang, Q. Roles of Integrins in Gastrointestinal Cancer Metastasis. Front. Mol. Biosci. 2021, 8, 708779. [CrossRef]

214. Gu, J.; Isaji, T.; Xu, Q.; Kariya, Y.; Gu, W.; Fukuda, T.; Du, Y. Potential roles of N-glycosylation in cell adhesion. Glycoconj. J. 2012, 29, 599–607. [CrossRef] [PubMed]

215. Isaji, T.; Sato, Y.; Zhao, Y.; Miyoshi, E.; Wada, Y.; Taniguchi, N.; Gu, J. N-glycosylation of the beta-propeller domain of the integrin alpha5 subunit is essential for alpha5beta1 heterodimerization, expression on the cell surface, and its biological function. J. Biol. Chem. 2006, 281, 33258–33267. [CrossRef]

216. Isaji, T.; Sato, Y.; Fukuda, T.; Gu, J. N-glycosylation of the I-like domain of beta1 integrin is essential for beta1 integrin expression and biological function: Identification of the minimal N-glycosylation requirement for alpha5beta1. J. Biol. Chem. 2009, 284, 12207–12216. [CrossRef]

217. Guo, H.B.; Lee, I.; Kamar, M.; Akiyama, S.K.; Pierce, M. Aberrant N-glycosylation of beta1 integrin causes reduced alpha5beta1 integrin clustering and stimulates cell migration. Cancer Res. 2002, 62, 6837–6845.

218. Sato, Y.; Isaji, T.; Tajiri, M.; Yoshida-Yamamoto, S.; Yoshinaka, T.; Somehara, T.; Fukuda, T.; Wada, Y.; Gu, J. An N-glycosylation site on the beta-propeller domain of the integrin alpha5 subunit plays key roles in both its function and site-specific modification by beta1,4-N-acetylglucosaminyltransferase III. J. Biol. Chem. 2009, 284, 11873–11881. [CrossRef]

219. Isaji, T.; Gu, J.; Nishiuchi, R.; Zhao, Y.; Takahashi, M.; Miyoshi, E.; Honke, K.; Sekiguchi, K.; Taniguchi, N. Introduction of bisecting GlcNAc into integrin alpha5beta1 reduces ligand binding and down-regulates cell adhesion and cell migration. J. Biol. Chem. 2004, 279, 19747–19754. [CrossRef]

220. Lu, J.; Isaji, T.; Im, S.; Fukuda, T.; Hashii, N.; Takakura, D.; Kawasaki, N.; Gu, J. β-Galactoside α2,6-sialyltransferase 1 promotes transforming growth factor-β-mediated epithelial-mesenchymal transition. J. Biol. Chem. 2014, 289, 34627–34641. [CrossRef]

221. Lu, J.; Isaji, T.; Im, S.; Fukuda, T.; Kameyama, A.; Gu, J. Expression of N-Acetylgalcosaminyltransferase III Suppresses α2,3-Sialylation, and Its Distinctive Functions in Cell Migration Are Attributed to α2,6-Sialylation Levels. J. Biol. Chem. 2016, 291, 5708–5720. [CrossRef] [PubMed]

222. Hang, Q.; Isaji, T.; Hou, S.; Wang, Y.; Fukuda, T.; Gu, J. A Key Regulator of Cell Adhesion: Identification and Characterization of Important N-Glycosylation Sites on Integrin α5 for Cell Migration. Mol. Cell. Biol. 2017, 37, e00558-16. [CrossRef] [PubMed]

223. Hang, Q.; Isaji, T.; Hou, S.; Im, S.; Fukuda, T.; Gu, J. Integrin α5 Suppresses the Phosphorylation of Epidermal Growth Factor Receptor and Its Cellular Signaling of Cell Proliferation via N-Glycosylation. J. Biol. Chem. 2015, 290, 29345–29360. [CrossRef] [PubMed]

224. Hang, Q.; Isaji, T.; Hou, S.; Zhou, Y.; Fukuda, T.; Gu, J. N-Glycosylation of integrin α5 acts as a switch for EGFR-mediated complex formation of integrin α5β1 to α6β4. Sci. Rep. 2016, 6, 33507. [CrossRef]

225. Ku, T.C.; Wu, M.H.; Yang, S.H.; Chen, S.T.; Hsu, T.W.; Jiang, T.; Liao, Y.Y.; Tien, Y.W.; Huang, M.C. C1GALT1 high expression is associated with poor survival of patients with pancreatic ducal adenocarcinoma and promotes cell invasiveness through integrin α(v). Oncogene 2021, 40, 1242–1254. [CrossRef]
226. Liang, C.; Fukuda, T.; Isaji, T.; Duan, C.; Song, W.; Wang, Y.; Gu, J. \(\alpha_1,6\)-Fucosyltransferase contributes to cell migration and proliferation as well as to cancer stemness features in pancreatic carcinoma. *Biochim. Biophys. Acta Gen. Subj.* 2021, 1865, 129870. [CrossRef]

227. Walser, M.; Umbricht, C.A.; Fröhli, E.; Nanni, P.; Hajnal, A. \(\beta\)-Integrin de-phosphorylation by the Density-Enhanced Phosphatase DEP-1 attenuates EGFR signaling in *C. elegans*. *PLoS Genet.* 2017, 13, e1006592. [CrossRef]