

Review

# Role of Integrins in Resistance to Therapies Targeting Growth Factor Receptors in Cancer

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**Abstract:** Integrins contribute to cancer progression and aggressiveness by activating intracellular signal transduction pathways and transducing mechanical tension forces. Remarkably, these adhesion receptors share common signaling networks with receptor tyrosine kinases (RTKs) and support their oncogenic activity, thereby promoting cancer cell proliferation, survival and invasion. During the last decade, preclinical studies have revealed that integrins play an important role in resistance to therapies targeting RTKs and their downstream pathways. A remarkable feature of integrins is their wide-ranging interconnection with RTKs, which helps cancer cells to adapt and better survive therapeutic treatments. In this context, we should consider not only the integrins expressed in cancer cells but also those expressed in stromal cells, since these can mechanically increase the rigidity of the tumor microenvironment and confer resistance to treatment. This review presents some of these mechanisms and outlines new treatment options for improving the efficacy of therapies targeting RTK signaling.

**Keywords:** integrin; focal adhesion kinase; therapy resistance; tyrosine kinase inhibitors; cancer-associated fibroblasts; mechanotransduction; EGFR; c-MET

## 1. Introduction

Many tumors initially respond to targeted therapies before resistance appears. The mechanisms that sustain tumor cells between initial response and disease progression are not well understood. Understanding drug resistance is urgently needed in cancer therapy. The interaction between cancer cells and the microenvironment (the extracellular matrix (ECM), fibroblasts, endothelial cells, and immune cells) is essential to cell survival, proliferation and migration [1,2]. Be it through physiological mechanisms or remodeling after therapy, the tumor microenvironment provides a safe haven that promotes the emergence of resistance.

The ECM alone can induce tumor cell resistance to treatment [3]. Integrins, a family of cell surface receptors, play an important role in the interaction with the ECM. The integrin family comprises 24 different receptors made up of heterodimers of 18 alpha ( $\alpha$ ) and 8 beta ( $\beta$ ) subunits, each of which binds to one or more ECM ligands. Integrins are involved in cellular adhesion to the ECM and in intercellular cohesion. Integrin biochemical and mechanical signaling regulates cell survival, proliferation, differentiation, migration, adhesion, apoptosis, anoikis, polarity and stemness [4–6]. Since integrins do not have enzymatic activity, once they bind to a ligand, they recruit cytoplasmic kinases such as focal adhesion kinases (FAKs). These, once recruited, autophosphorylate and present a docking site for the proto-oncogene tyrosine-protein kinase Src [7]. The FAK/Src complex activates the NF- $\kappa$ B (nuclear factor- $\kappa$ B), MAPK (mitogen-activated protein kinase) and PI3K (phosphoinositide

3-kinases) pathways. These signaling pathways are redundant with the receptor tyrosine kinase (RTK) signaling pathways. RTKs are families of surface receptors with tyrosine kinase activity that bind to growth factors, cytokines and hormones. RTK signaling pathways regulate cell growth, differentiation, metabolism and apoptosis in response to growth factor stimulation of cross-activation by co-receptors such as integrins. In normal cells, RTK function is tightly regulated. However, in cancer, mutations, overexpression, autocrine/paracrine stimulation and aberrant degradation lead to RTK constitutive activation and consequently to tumor formation and progression [8,9].

Integrins cooperate with several RTKs, such as epidermal growth factor receptor (EGFR), c-Met, platelet-derived growth factor receptor (PDGFR), insulin-like growth factor receptor (IGFR) and vascular endothelial growth factor receptor (VEGFR). This cooperation promotes solid tumor progression and aggressiveness as well as contributing to therapy resistance, be it to chemotherapy, radiotherapy or targeted therapy. Integrin/RTK crosstalk has been well described in several reviews [4,5]. In recent decades, integrins have emerged as new players in resistance to RTK-targeted therapies. The purpose of this review is to present a synthesis of the literature and to explore the diversity of the mechanisms by which integrins are able to counteract RTK-targeted therapies (Table 1). New promising therapeutic approaches resulting from these discoveries will be also discussed.

**Table 1.** Cases of integrin-mediated resistance to RTK-targeted therapies cited in this review.

RTK	Therapies Targeting RTK	Type of Tumor	Experimental Model	Patient Data	Integrin Modulation	Mechanisms of Resistance	Ref
<b><math>\beta</math>1 integrin</b>							
EGFR	Cetuximab	Head and neck squamous cell carcinoma	A549 cells	-	Cetuximab-induced fibronectin overexpression. siRNA-mediated depletion of $\beta$ 1 and $\alpha$ 5	Cetuximab enhances p38/ATF2-dependent fibronectin production and the activation of the focal adhesion kinase (FAK)/Erk pathway. siRNA-mediated depletion of $\beta$ 1 and $\alpha$ 5 integrin decreases the cell survival of cetuximab-treated cells.	[10]
EGFR	Cetuximab	Pancreatic cancer	Miapaca-2, Capan-2, SW1990 AsPC-1, BXPc-3, PANC-1	-	-Endogenous overexpression of $\beta$ 1 integrin in resistant cells -siRNA-mediated depletion of $\beta$ 1	$\beta$ 1 overexpression in resistant cells stimulates Src and Akt pathways. Extracellular matrix (ECM)-independent activation of $\beta$ 1 is mediated by its interaction with neuropilin-1. siRNA-mediated depletion of $\beta$ 1 or inhibition of $\beta$ 1/neuropilin-1 interaction increases cetuximab cell toxicity.	[11]
EGFR	mAb225	Colon cancer	Caco-2	-	Plasmid-induced $\alpha$ 5 overexpression	Fibronectin stimulation of $\alpha$ 5-expressing cells overrides mAb225-mediated cell growth inhibition. Integrin activates epidermal growth factor receptor (EGFR) kinase and the mitogen-activated protein kinase (MAPK) pathway.	[12]
EGFR	Gefitinib Erlotinib	Lung cancer	PC-9 and 11-18	Patient samples	-Endogenous overexpression of $\beta$ 1 integrin in resistant cells and tumors -siRNA-mediated depletion of $\beta$ 1	siRNA-mediated silencing of $\beta$ 1 restores Erlotinib potency to inhibit cell proliferation and the Src and Akt pathways.	[13]
EGFR	PD1530335 (AG1517)	Glioma	Glioma stem-like cells (GSCs) isolated from glioblastoma (GBM) surgical pieces	-	Lentiviral-mediated $\beta$ 1 overexpression	Delocalization of $\beta$ 1 integrin from lipid raft sensitizes GSC to tyrosine kinase inhibitor (TKI)-induced apoptosis. $\beta$ 1 overexpression protects GSC from apoptosis in a FAK-dependent manner.	[14]

Table 1. Cont.

RTK	Therapies Targeting RTK	Type of Tumor	Experimental Model	Patient Data	Integrin Modulation	Mechanisms of Resistance	Ref
HER2	Trastuzumab Lapatinib	Breast cancer	HER2+ cells (BT474, HCC1954)	-	-Endogenous overexpression of $\beta 1$ integrin in resistant cells. -siRNA-mediated depletion of $\beta 1$ and function-blocking mAb	Overexpression of $\beta 1$ enhances FAK and Src phosphorylation. Silencing or functional inhibition of $\beta 1$ integrin sensitizes cells to HER-2 inhibition (cell proliferation, apoptosis, clonogenic assays) in a FAK-dependent way.	[15]
HER2	TPB (trastuzumab + pertuzumab + burparlisib)	Breast cancer	Tumors cells derived from HER2+/PIK3CAH <sup>1047R</sup> mice, MDA-MB453, HCC1954 cell lines	Patient samples and data	-Endogenous overexpression of collagen II in resistant tumors - $\beta 1$ function-blocking mAb	Resistance to anti-HER2 tritherapy activates $\beta 1$ integrin and Src pathways. Inhibition of $\beta 1$ /Src blocks coll II-induced resistance to TPB (cell growth, cell survival)	[16]
VEGFR	Bevacizumab	Glioma	U87, bevacizumab-resistant cell lines derived from surgical pieces (in vitro and xenografts)	Patient samples and data	-Endogenous overexpression of $\beta 1$ integrin in resistant cells. -shRNA-mediated depletion of $\beta 1$ and function-blocking mAb	Bevacizumab induces hypoxia that is associated with increased $\beta 1$ and FAK expression. $\beta 1$ inhibition (function-blocking mAb) results in increased cell apoptosis and in disrupted tumor mass formation in the treated tumor	[17]
VEGFR	Bevacizumab	Glioblastoma breast cancer	PDX for bevacizumab-resistant human GBM GBM and breast cancer cells	Patient samples	Increased $\beta 1$ /c-Met complex formation in bevacizumab-resistant tumors	Vascular endothelial growth factor receptor (VEGFR)-2 activation impedes $\beta 1$ /cMet complex formation. Resistance to antiangiogenic therapy increased $\beta 1$ /cMet complex formation and cross-activation of both receptors.	[18]
<b><math>\beta 3</math> integrin</b>							
EGFR	Erlotinib Lapatinib	Lung cancer	A549 and H23 xenograft	Patient samples	shRNA-mediated depletion of $\beta 3$	EGFR TKI treatment induces selection of $\beta 3$ -positive cancer stem cells. Integrin $\beta 3$ (in a ligand-independent way) interacts with galectin-3 to promote KRAS/RalB/NFkB activation, thereby promoting cell survival.	[19]

Table 1. Cont.

RTK	Therapies Targeting RTK	Type of Tumor	Experimental Model	Patient Data	Integrin Modulation	Mechanisms of Resistance	Ref
IGFR	Linsitinib	Pancreatic cancer	Panc-1 and FG xenograft	-			
EGFR	Gefitinib	Lung cancer	HCC827	-	-Epigenetic silencing of $\beta$ 3-targeting miR-489-3p in resistance cells -Lentivirus-mediated expression of $\beta$ 3 -Inhibitor or mimic of miR-489-3p	Hypermethylation of miR-483-3p in resistant cells activates the $\beta$ 3-dependent FAK/Erk pathway to promote cell survival and EMT	[20]
IGFR	Cixutumumab	Head and neck squamous cell carcinoma	Several cell lines	Patient samples	shRNA-mediated depletion of $\beta$ 3 and function-blocking mAb	Upon cixutumumab treatment, insulin-like growth factor (IGF)-1 directly binds to integrin $\alpha$ v $\beta$ 3, increasing Src/Akt-dependent proliferation and survival.	[21]
		Lung cancer	686LN, UMNSCC38, H226B, A549 In vitro and xenograft	-			
PDGFR, VEGFR, FGFR	Sorafenib	Acute myeloid leukemia	MV4-11	Patient samples and data	-Endogenous overexpression of $\beta$ 3 integrin in resistant cells - $\beta$ 3 function-blocking mAb	Activation of $\beta$ 3/PI3K/Akt/GSK3 $\beta$ / $\beta$ -catenin pathway reduces apoptotic level and increases cell proliferation in resistant cells	[22]
PDGFR, VEGFR, FGFR	Sorafenib	Hepatic cancer	Huh-7, Hep3B, SK-Hep-1, HepG2, PLC/PRF/5	-	-shRNA-mediated depletion of $\beta$ 3	Forced expression of galectin-1 elevates $\beta$ 3 expression and activates the FAK/PI3K/Akt pathway to trigger EMT. This is correlated with an increased resistance to sorafenib in galectin-1 expressing cells.	[23]
<b><math>\beta</math>4 integrin</b>							
HER2	Gefitinib	Breast cancer	Murine model mammary gland MMTV-Neu (YD)	-	-Forced expression of $\beta$ 4 mutant (depleted from its signaling domain)	$\alpha$ 6 $\beta$ 4/ErbB2 complex activates transcription factor STAT3 and c-Jun to promote cancer progression. The signaling domain of $\beta$ 4 is required to trigger gefitinib resistance by an unknown mechanism, whereas ErbB2, C-Jun and STAT3 phosphorylation is still inhibited by gefitinib.	[24]
HER2	Trastuzumab Lapatinib	Breast cancer	BT474, ZR-75-1, SKBR3, MD-MB-453	-	shRNA-mediated depletion of $\alpha$ 6 $\beta$ 4 and function-blocking mAbs	Integrin-mediated adhesion to laminin-5 promotes resistance to anti-ERB2 therapies. Removal of CD151 (an integrin co-receptor) or FAK sensitizes cells to drugs (cell proliferation)	[25]
EGFR	Gefitinib	Gastric cancer	SGC7901	Patient samples	-Endogenous overexpression of $\alpha$ 6 $\beta$ 4 integrin in resistant cells -siRNA-mediated depletion of $\alpha$ 6 $\beta$ 4	Endogenous or forced expression of $\beta$ 4 integrin promotes gefitinib resistance (cell proliferation and apoptosis). $\beta$ 4 expression is correlated with a decrease in p-EGFR protein levels.	[26]
EGFR	Gefitinib	Hepatic cancer	HLE, Alexander, HepG2, Sk-Hep1	-	Laminin-332 expression	Lm-332-dependent activation of integrin dampens gefitinib effectiveness in cell proliferation survival and apoptosis assays. Lm-332 potentiates the activation of Akt in gefitinib-treated cells.	[27]

Table 1. Cont.

RTK	Therapies Targeting RTK	Type of Tumor	Experimental Model	Patient Data	Integrin Modulation	Mechanisms of Resistance	Ref
FAK							
EGFR	Erlotinib	Lung cancer	A549, H1299, H1975, HCC827, HCC4006 Xenograft of A549	-	FAK inhibitors	Combination of FAK inhibitors and erlotinib is more potent than a single agent to reduce cell viability (2D and 3D models), to increase the apoptosis pathway and cell cycle arrest in resistant cells, and to reduce tumor growth in vivo. The sensitization of erlotinib by FAK inhibitors is associated with a strong inhibition of Akt.	[28]
EGFR	Erlotinib Osimertinib	Lung cancer	PC-9, H1975, HCC827, HCC4006, H3255, 11-18 cell lines PC-9 xenografts	-	FAK inhibitor	Activation of FAK and Src family kinases (SFK) pathways attenuates the efficiency of EGFR therapies presumably via the sustained activation of MAPK and Akt pathways. Concomitant inhibition FAK, Src and EGFR inhibitors potently inhibit MAPK and Akt pathways and cell proliferation.	[29]
EGFR	Afatinib Erlotinib Osimertinib	Lung cancer	PC-9, HCC827 Established TKI-resistant cells	-	siRNA-mediated depletion of FAK and inhibitor	Compensatory activation of SFKs, FAK and Akt is observed in TKI-resistant cells. FAK inhibition increased afatinib efficacy to inhibit cell survival and cell migration.	[30]
EGFR	Erlotinib	Lung cancer	H1299, H1650 cell lines H358 cell line and xenograft	-	siRNA-mediated depletion of FAK and inhibitor (PF-562271)	Mass spectrometry analysis revealed an aberrant phosphorylation of FAK in erlotinib-resistant cells. Inhibition of FAK led to a decrease in cell survival in erlotinib-treated cells.	[31]

## 2. $\beta$ 1 Integrins

$\beta$ 1 integrins form heterodimers with no less than 12 of the 18 known alpha subunits, and thus represent the largest integrin subgroup.  $\beta$ 1 integrins are overexpressed in solid tumors such as breast carcinoma, lung carcinoma and head and neck squamous cell carcinoma (HNSCC) [32–34]. In cancer cells,  $\beta$ 1 integrins are associated with proliferative signaling, trigger cell death resistance, induce angiogenesis and activate cell migration and the metastatic cascade [35–39].  $\beta$ 1 integrins contribute to chemotherapy resistance [38,40–50] and promote radiotherapy resistance in HNSCC [51–54], breast carcinoma [55,56], laryngeal carcinoma [57,58], and glioma [59,60]. Based on these observations,  $\beta$ 1 integrin antagonists such as small molecules (ATN-161, JSM6427) or function-blocking antibodies (volociximab, OS2966) have been considered as potential therapeutic approaches [32].

### 2.1. $\beta$ 1 Integrins Promote Resistance to EGFR-Targeted Therapies

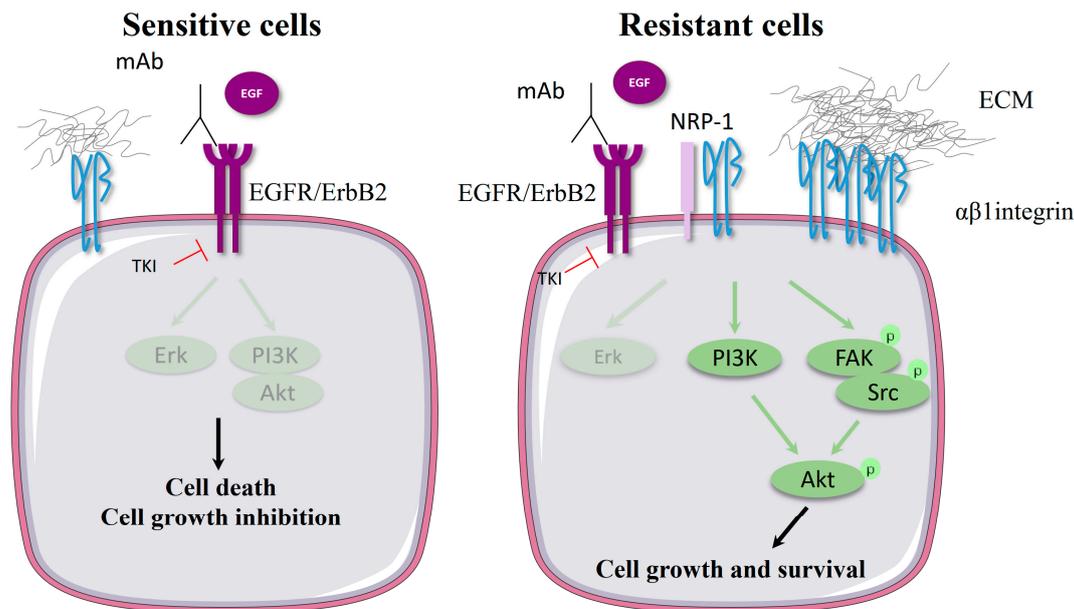
#### 2.1.1. Cooperation between $\beta$ 1 Integrin and EGFR in Cancer Cells

EGFR was the first growth factor receptor reported as being activated in normal cells by  $\beta$ 1 integrin adhesion to fibronectin, with or without the presence of EGF [61,62]. In cancer cells,  $\beta$ 1 integrin potentiates EGF-mediated EGFR autophosphorylation in vitro and in vivo [38].  $\beta$ 1 integrin also regulates EGFR membrane trafficking and so modulates its oncogenic signaling activity [63]. In human ovarian carcinoma cells,  $\alpha$ 5 $\beta$ 1 coordinates EGFR recycling to the plasma membrane in a way that enhances EGFR-Tyr845 phosphorylation and the serine kinase Akt downstream pathway, thus promoting cell invasion [64]. In lung carcinoma cells, the level of  $\beta$ 1 integrin expression regulates the cell surface expression of EGFR and sustains its endocytic pathway [38]. It should be noted that although the literature has mostly described  $\beta$ 1 integrins as positive regulators of EGFR, the relationship between integrin and EGFR appears to be far more complex. For instance,  $\alpha$ 5 $\beta$ 1 has been described as restricting EGFR membrane localization and responsiveness to EGF stimulation [65], while  $\alpha$ 1 $\beta$ 1 inhibits EGFR signaling by activating the protein phosphatase TCPTP (T-cell protein tyrosine phosphatase) [66].  $\beta$ 1 integrin/EGFR interaction was initially suggested by co-immunoprecipitation and confocal experiments, and FRET analysis revealed potential direct physical interaction between  $\beta$ 1 integrin and either EGFR [59,67] or HER2 (ErbB2) [68]. Studies on  $\beta$ 1 integrin cooperation with EGFR have revealed new avenues for improving the effectiveness of radiotherapy. Indeed, EGFR/ $\beta$ 1 complex formation is a prognostic factor for radiotherapy resistance in glioma [59]. The importance of EGFR/ $\beta$ 1 integrin cooperation in radiotherapy resistance has been confirmed by experiments which have shown that co-targeting the two of them radiosensitizes cancer cells [10,53]. Whole exome analysis has identified mTOR and KEAP1 as potential genetic biomarkers and molecular targets for radiosensitizing HNSCC [69]. By contrast, concomitant inhibition of  $\beta$ 1 integrin and EGFR in HNSCC spheroids [70] and colon carcinoma [71] does not improve radiotherapy efficacy.

#### 2.1.2. Molecular Mechanism of $\beta$ 1 Integrin-Mediated Resistance to EGFR-Targeted Therapies

The most common type of lung cancer is non-small cell lung carcinoma (NSCLC), and it is characterized by EGFR overexpression. Several oral tyrosine kinase inhibitors (TKIs) targeting EGFR are used in clinical practice for treating NSCLC, including gefitinib, erlotinib, afatinib, dacomitinib and osimertinib. These drugs show some efficacy, but NSCLC eventually relapses. Resistance to treatment is caused either by T790M EGFR mutation, which impedes TKIs (except osimertinib) from binding to EGFR by increasing its affinity to ATP, or by the activation of alternative or downstream signaling pathways [72]. Several groups independently report that acquired resistance to gefitinib has correlated with  $\beta$ 1 integrin overexpression in NSCLC cells [13,73,74] or in lung tumor samples from patients refractory to gefitinib or erlotinib [13]. Interestingly, these studies revealed that  $\beta$ 1 integrin overexpression occurs in NSCLC cells that do or do not harbor EGFR T790M mutations, irrespective of EGFR-phosphorylation level. Both antibody-mediated functional inhibition and siRNA-mediated silencing of  $\beta$ 1 integrin sensitize

NSCLC to TKIs in vitro and in vivo [13,38,73], demonstrating that  $\beta 1$  integrin is instrumental in TKI resistance. Conversely, the vector-mediated overexpression of  $\beta 1$  integrin protects cancer cells from TKI-induced cell growth inhibition [14,38]. Downstream of the  $\beta 1$ /PI3K and  $\beta 1$ /Src/FAK pathways, the serine kinase Akt plays a pivotal role in resistance to gefitinib or erlotinib (Figure 1) [13,38,73,75]. FAK is an essential protein in integrin/growth factor receptor crosstalk and could be a valuable target for sensitizing cancer cells to TKIs [76]. Integrin-dependent FAK activation decreased cancer cells' sensitivity to anti-EGFR drugs [10,14]. A series of studies confirmed the importance of FAK signaling in resistance to first- (erlotinib), second- (afatinib) and third-generation (osimertinib) EGFR TKIs [28–31].



**Figure 1.**  $\beta 1$  integrin induces EGFR- or HER (ErbB2)-targeted therapy resistance. In sensitive cells, the inhibition of the ErbB receptor family by either antibodies or tyrosine kinase inhibitors (TKIs) blocks Erk and Akt pathway activation leading to cell death and cell growth inhibition. In resistant cells,  $\beta 1$  integrin or its associated extracellular matrix (ECM) proteins are often overexpressed, leading to the activation of  $\beta 1$ -downstream pathways such as PI3K or FAK/Src. These pathways converge to activate the serine kinase Akt that promotes cell survival and cell growth. Alternatively,  $\beta 1$  integrin can be activated by coreceptors such as neuropilin-1 (NRP-1) to trigger EGFR-targeted therapy resistance independently of integrin-mediated cell adhesion.

$\beta 1$  integrins can also trigger resistance to antibody-mediated EGFR inhibition. In colon carcinoma cells, the fibronectin/ $\alpha 5\beta 1$  axis overcomes the inhibition of EGFR-mediated cell growth by mAb225, the murine form of the chimeric anti-EGFR antibody cetuximab [12]. In lung carcinoma cells, cetuximab activates the p38/ATF2 pathway. This enhances fibronectin synthesis, which in turn dampens cetuximab's cytotoxic effect both in vitro and in xenografted mice.  $\alpha 5\beta 1$  integrin-silencing sensitized NSCLC cells to cetuximab monotherapy, showing that  $\alpha 5\beta 1$  integrin-mediated adhesion to fibronectin plays an essential role in reducing cetuximab activity in lung carcinoma cells [10,53]. In pancreatic ductal adenocarcinoma cells, the overexpression of  $\beta 1$  activates the FAK/Src/Akt pathway, triggering EGFR ligand-independent cell growth and thus bypassing cetuximab antagonist activity [11].

## 2.2. $\beta 1$ Integrins Promote Resistance to Therapies Targeting HER2

HER2 (ErbB2) is another member of the EGFR family with intrinsic tyrosine kinase activity and is devoid of a ligand-binding domain. Overexpressed in nearly 30% of breast cancers, HER2 plays an important role in cancer progression. It is a highly attractive target for treatment with trastuzumab or pertuzumab, two humanized HER2-targeted antibodies, or for treatment with lapatinib, a TKI. Despite the radical improvement in the prognosis of HER2+ breast cancer brought about by these

drugs, most patients with HER2+ tumors relapse and progress within a few years [77]. Using a genetic approach in mice,  $\beta 1$  integrin expression has been shown to play a critical role in HER2– induced breast tumor progression but is not required for tumor formation [78]. An immunochemical analysis of clinical samples revealed that  $\beta 1$  integrin overexpression is a negative prognostic factor for patients with HER2+ breast cancer being treated with trastuzumab [68]. In vitro,  $\beta 1$  integrin is overexpressed in HER2+ breast tumor cells with de novo resistance to trastuzumab.  $\beta 1$  integrin knockdown by siRNA silencing or inhibition by function-blocking antibody therapy enhanced drug efficacy by inhibiting the Erk1,2 and Akt pathways [79]. In contrast, another report showed that HER2+ breast cancer cell lines with de novo resistance to trastuzumab were not sensitized by  $\beta 1$  integrin inhibition, presumably because they maintain HER2 hyperphosphorylation. However, in the same study,  $\beta 1$  integrin was shown to promote resistance to lapatinib/trastuzumab treatment via an upregulation of FAK and Src. In that setting, antibody-mediated inhibition of  $\beta 1$  integrin decreased the 3D-growth and survival of the resistant cells being treated [15]. HER3, a kinase-dead member of the EGFR family, regulates HER2 signaling by initiating ligand-induced HER2 activation in the HER2-HER3 heterodimer. Co-targeting HER3 (via siRNA-mediated silencing) and  $\beta 1$  integrin (via a function-blocking antibody) is more effective in controlling tumor growth in mice than the dual inhibition of HER2 (lapatinib) and  $\beta 1$  integrin (antibody) [80].

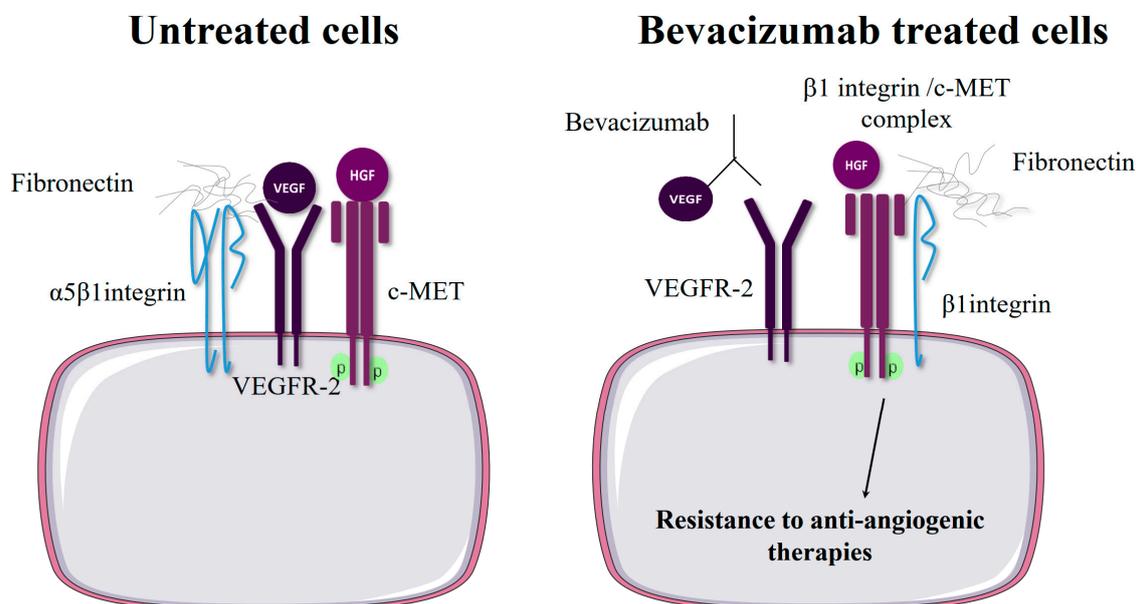
The tumor microenvironment may markedly affect the response to HER2– targeted therapy [3]. Laminin-332, a ligand of integrins  $\alpha 6\beta 4$ ,  $\alpha 6\beta 1$  and  $\alpha 3\beta 1$ , is lost during the malignant transformation of breast cancer but remains expressed by normal tissue and may thus support the initial transition to invasive cancer. Integrin-dependent adhesion to laminin-332 elicits lapatinib and trastuzumab resistance in HER2+ human breast tumor cell lines [25]. Recently, Hanker and colleagues used genetic engineering of HER2+/PIK3CA<sup>H1047R</sup> mice to generate tumors resistant to TPB treatment (trastuzumab + pertuzumab + burparlisib, a PI3K inhibitor). Whole genome sequencing did not reveal any acquired mutation that could explain the acquired resistance to TPB. RNA-seq analysis did reveal the upregulation of several ECM genes, including Col2a1, which codes for the collagen type II alpha 1 chain. Collagen II activates the  $\beta 1$  integrin/Src pathway, promoting tumor resistance to TPB. In clinical settings, collagen II expression on immunohistochemical analysis correlates with a poor response to HER2– targeted therapies [16]. Antibody-drug conjugates (ADCs) are a promising novel class of therapeutic agents that combine a cytotoxic agent with the antigenic selectivity of an antibody. Ado-trastuzumab emtansine (T-DM1) is an ADC consisting of trastuzumab and DM1, a microtubule inhibitor [81]. Despite a good initial response to the drug, most patients eventually relapse due to acquired resistance. Recent reports have documented alterations in the ECM/integrin pathway in T-DM1-resistant cancer cells [82,83], which represent promising new approaches to enhancing T-DM1 toxicity against cancer cells.

### 2.3. $\beta 1$ Integrin Expression Confers Resistance to Anti-Angiogenic Therapies Targeting VEGFR or c-Met

Tumor neo-angiogenesis is the formation of new blood vessels from those pre-existing in the tumor. Neo-angiogenesis is a critical step in tumor progression as it enhances tumor growth and cancer cell metastasis. The concept of anti-angiogenic therapy, i.e., inhibiting pro-angiogenic factors, has remained disappointing, in part due to acquired resistance [84]. The role of integrin in endothelial cell migration and survival and in angiogenesis has been widely described [85]. Several reports indicate that  $\beta 1$  integrin plays a part in anti-angiogenic therapy resistance [35,86]. Bevacizumab, a humanized antibody against VEGF-A, was the first anti-angiogenic drug used in clinical practice [87]. Micro-array analysis revealed that a subset of bevacizumab-resistant glioblastomas (GBMs) harbor  $\alpha 5$  integrin and fibronectin overexpression [88], likely due to hypoxia provoked by bevacizumab treatment [17]. The inhibition of  $\beta 1$  integrin could become a treatment avenue in the future, as  $\beta 1$  integrin knockdown in bevacizumab-resistant glioma cells prevents in vivo growth while OS2966, a  $\beta 1$  function-blocking antibody, potentiates bevacizumab therapy [17].

The hepatocyte growth factor (HGF)/c-Met pathway plays an important role in tumor angiogenesis as well as in the development of resistance to VEGFR inhibition by TKIs [89].  $\beta$ 1 integrin and c-Met are able to form a complex and drive mutual ligand-independent cross-activation [18,90], indicating that  $\beta$ 1 integrin and c-Met crosstalk may represent an adaptive mechanism to anti-angiogenic therapies. C-Met and  $\beta$ 1 integrin membrane trafficking are closely related. In vascular endothelial cells, HGF stimulates  $\beta$ 1 integrin recycling to promote cell spreading, focal adhesion formation, cell migration and tumor angiogenesis [91]. Moreover, c-Met can induce  $\beta$ 1 integrin endocytosis [92], and integrin can transmit cell survival signaling from early endosomes [93]. The serine–threonine kinase MAP4K4 activates  $\beta$ 1 integrin and mediates the accumulation of activated c-Met in cytosolic vesicles [94]. Thus,  $\beta$ 1 integrin/c-Met ligand-independent cooperation is not restricted to the cell surface and can occur in autophagy-like endosomal compartments [95]. Because VEGFR-2 activation sequesters  $\beta$ 1 integrin from c-Met in patients, the  $\beta$ 1 integrin/c-Met complex is associated with bevacizumab resistance in GBM. It is interesting to note that OS2966 can reduce the formation of the  $\beta$ 1 integrin/c-Met complex [18], which could explain its anti-angiogenic activity in bevacizumab-resistant tumors [17]. Targeting  $\beta$ 1 integrin/c-Met complex formation may open up new treatment options for overriding resistance to targeted therapy and so limiting tumor angiogenesis as well as c-Met-mediated cell growth [75].

It seems clear that  $\beta$ 1 integrins play a pivotal role in resistance to RTK-targeted therapies both in vitro and in vivo. The pharmacological manipulation of integrins [14,15,18,79,80] or downstream signaling molecules such as FAK or Akt [51–54,58–61] has shown some efficacy in preclinical models and may offer promising new avenues to sensitizing cancer cells to anti-RTK therapies.  $\beta$ 1 integrin expression levels could also represent a potent biomarker for stratifying patients likely to derive greater benefit from anti-RTK therapy, but the search for a molecular complex such as  $\beta$ 1/EGFR,  $\beta$ 1/HER2 or  $\beta$ 1/c-Met could lead to even more promising strategies (Figure 2) [18,59,68].



**Figure 2.** Hypothetical model presenting how  $\beta$ 1/c-MET molecular complexes provide cancer cell resistance to anti-angiogenic therapies. In untreated cells, ligand-activated VEGFR-2 engages both  $\alpha$ 5 $\beta$ 1 integrin and c-MET, impeding their physical contact. In  $\alpha$ 5 $\beta$ 1 integrin-expressing cells, anti-angiogenic therapeutic intervention with bevacizumab decreases VEGF/VEGFR-2 binding.  $\beta$ 1/c-MET complex formation is thus promoted, which leads to the cross-activation of both receptors and the activation of the downstream AKT signaling pathway (adapted from [18]).

In solid tumors, resistance to targeted therapies can be mediated by  $\beta$ 1 integrin via a wide diversity of mechanisms that may require ligand-dependent or -independent integrin functions, or  $\beta$ 1

integrin interaction with RTKs or with other co-receptors. The clinical relevance of the in vitro and vivo studies was mainly evident in glioma and breast cancers. Even with the promising therapeutic role of  $\beta 1$  integrin, it is important to keep in mind the complexity of integrin functions and the fact that the  $\alpha$  subunits involved in the process remain indeterminate most of the time, although we know their importance in integrin function. The present data could also benefit from a patient stratification, allowing decreased doses of targeted therapy and consequently fewer secondary effects.

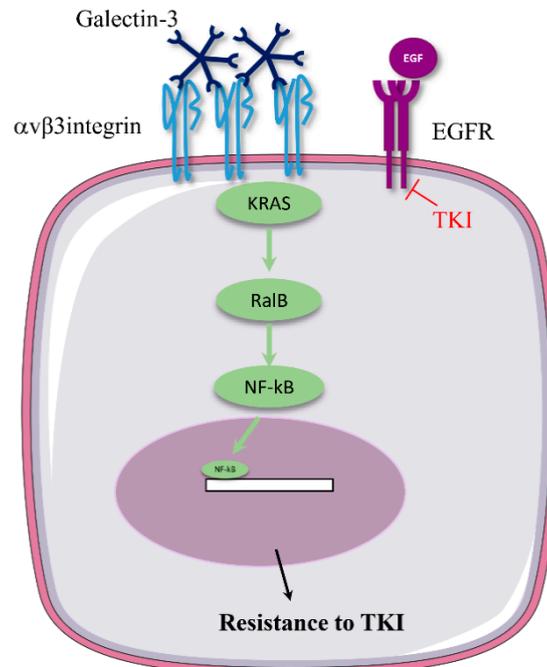
### 3. $\alpha v\beta$ Integrins

$\alpha v\beta$  integrins are a large family of integrins ( $\alpha v\beta 3$ ,  $\alpha v\beta 5$ ,  $\alpha v\beta 6$  and  $\alpha v\beta 8$ ).  $\alpha v$  integrins drive cancer progression and are upregulated either by cancer cells or endothelial cells in many solid tumors, including colon carcinoma, melanoma, and breast, lung, pancreatic and brain cancers.  $\alpha v\beta$  integrins are characterized by their capacity to recognize the RGD (arginine-glycine-aspartate) peptide sequence in a large variety of ligands (such as vitronectin, fibronectin and osteopontin) [96].  $\alpha v\beta$  integrin expression and activation drive the intracellular signaling that promotes cancer cell survival, invasion, metastasis, angiogenesis, and self-renewal [5,97], as well as chemotherapy resistance [98,99] and radiotherapy resistance [100–104]. Extensive preclinical studies have established  $\alpha v\beta 3$  inhibitors as potential new therapeutic tools [103,105–107], with several trials evaluating their efficacy in clinical settings as a result [108–110]. Cilengitide (EMD121974, Merck), a cyclic pentapeptide derived from the RGD sequence, was the most promising drug and was evaluated in clinical trials in newly diagnosed GBM. Unfortunately, these trials revealed that cilengitide did not improve the outcomes of patients receiving chemo- and radiotherapy [111–113], making it necessary to re-evaluate the treatment conditions or improve the molecular-based selection of patients who could benefit from cilengitide. Recently, Cosset and colleagues have shown that in GBM,  $\alpha v\beta 3$  integrin enhances the expression of the high-affinity glucose transporter GLUT3 via PAK4 (P21 Activated Kinase 4)/YAP (Yes-associated protein) pathway activation. The overexpression of GLUT3 increased tumor cell survival in a glucose-depleted environment. Furthermore, using genomic analysis the authors identified a subset of  $\alpha v\beta 3$ /GLUT3-expressing tumors that were addicted to GLUT3 as well as highly sensitive to cilengitide and function-blocking anti- $\alpha v$  antibodies [114].

#### 3.1. $\alpha v$ Integrin Triggers Resistance to Anti-EGFR Therapies

The work of Seguin and colleagues paved the way for the demonstration of a pivotal role for  $\alpha v\beta 3$  integrin in resistance to EGFR-targeted therapy [19]. They first established that  $\alpha v\beta 3$  integrin was selectively expressed by tumor-initiating cells from lung and pancreatic carcinoma patient-derived-xenografts (PDXs). More strikingly,  $\beta 3$  expression drove lung and pancreatic cancer cell resistance to TKIs targeting EGFR (erlotinib and lapatinib) both in vitro and in mice. Conversely, the short hairpin RNA-mediated depletion of  $\beta 3$  sensitized cells to the TKIs. In fact, TKI treatment of human PDX tumors led to the selection of  $\beta 3$ -positive cells that acquired stem cell-like and resistant phenotypes. Mechanistically,  $\beta 3$  integrin activates the KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog)/Ra1B (Ras-like proto-oncogene B)/NF- $\kappa$ B pathway. It is important to note that the activation of this pathway is independent of the canonical FAK pathway and of integrin/ECM interaction. While this is surprising at first glance, the same group had already observed that  $\alpha v\beta 3$  integrin could promote tumor progression independently of ligand binding and FAK activation [115]. The authors discovered that the recruitment of KRAS and the consequent activation of Ra1B by  $\beta 3$  required  $\beta 3$  binding to galectin-3, a cell adhesion protein with a specific affinity for  $\beta$ -galactoside glycoconjugates (Figure 3).  $\beta 3$  integrin may also play a pivotal role in mutant KRAS oncogenic function [116]. In a subset of lung and pancreatic adenocarcinomas addicted to mutant KRAS, the disruption of galectin-3/ $\beta 3$  interaction by GCS-100, a galectin-3 antagonist currently under clinical development [117], released mutant KRAS from  $\beta 3$  and inhibited tumor growth in mice. While these results may suggest that GCS-100 could sensitize lung cancer cells to TKIs, the authors have not yet explored this possibility. A growing body of data indicates that microRNA (miRNA)

dysregulation modulates gefitinib resistance in lung carcinoma [118–124]. In gefitinib-resistant cells, a miRNA targeting the 3'-UTR of  $\beta 3$  integrin (miR-483-3p) is silenced by epigenetic methylation. The forced overexpression of  $\beta 3$  integrin can restore gefitinib resistance in miR-483-3p-expressing cells through the activation of a  $\beta 3$ /FAK/ERK pathway and epithelial to mesenchymal transition induction [20].



**Figure 3.**  $\beta 3$ /KRAS/RalB/NF $\kappa$ B pathway mediates EGFR-targeted therapy resistance. In EGFR TKI-treated tumors, cells overexpressing  $\alpha v \beta 3$  integrin are selected, leading to a resistant tumor. By binding to oligosaccharide moieties of  $\beta 3$  integrin, galectin-3 promotes integrin/KRAS interaction independently of integrin-mediated adhesion to ECM proteins. KRAS activates the downstream RalB/NF $\kappa$ B pathway that leads to therapy resistance by promoting a stem cell-like phenotype (adapted from [19]).

The role of  $\alpha v$  integrin in resistance to anti-EGFR therapy has been assessed in clinical settings. Cilengitide has been evaluated in combination with cetuximab in two phase II clinical trials on HNSCC and NSCLC [125]. Cilengitide did not improve patient outcomes. However, *ex vivo* experiments on patient-derived samples showed that a subset of sensitive tumors could be selected based on the inhibition of colony formation or cytokine release [126,127]. The phase I/II Poseidon trial explored the efficacy of a combination treatment using abituzumab, an  $\alpha v$  integrin inhibitor, and cetuximab in KRAS wild-type metastatic colorectal cancer. Again, the trial did not reach the primary phase II endpoint, but the authors did observe that patients overexpressing  $\alpha v \beta 6$  integrin might benefit from the abituzumab/cetuximab plus irinotecan combination treatment compared to cetuximab plus irinotecan alone [128]. In the future, therefore, reliable biomarkers may emerge for selecting patients likely to benefit from the synergy between  $\alpha v$  integrin and EGFR inhibition.

### 3.2. $\alpha v \beta 3$ Integrin Involvement in Resistance to Drugs Targeting Other RTKs

Insulin-like growth factors and their cognate receptors are important in cancer progression [129]. Antibody-based therapy against IGF-1R has shown limited efficacy in phase II/III clinical trials [130].  $\alpha v \beta 3$  integrin enhances IGF-1R signaling activity through the joint ligand-dependent activation of both receptors. However, another model of crosstalk has been proposed in which the IGF-1R ligand, IGF-1, directly binds to the  $\beta 3$  integrin subunit and promotes the anchorage-independent formation of a  $\beta 3$ /IGF-1/IGF-1R ternary complex [131–134].  $\alpha v \beta 3$  integrin significantly contributes to resistance to

IGF-1R-targeted TKIs [19]. In HNSCC and NSCLC, during treatment with cixutumumab, a humanized anti-IGF-1R antibody, the Src/Akt pathway is activated by IGF-1/ $\beta$ 3 integrin interaction independently of cell/ECM interaction. The molecular targeting of  $\beta$ 3 integrin increased cixutumumab's efficacy both in vitro and in mice [21]. While these preclinical data are encouraging, the role of the  $\beta$ 3/Src pathway in resistance to anti-IGFR treatment has not yet been evaluated in clinical settings.

Sorafenib is a multikinase inhibitor for treating hepatocellular, kidney and thyroid carcinomas [135]. According to KINOMEScan data from the Library of Integrated Network-based Cellular Signatures project (<http://lincs.hms.harvard.edu/>), among the numerous kinases inhibited by sorafenib are the receptors for PDGF, VEGF and fibroblast growth factor. In acute myeloid leukaemia,  $\alpha$ v $\beta$ 3 integrin expression is a negative prognostic factor and is associated with a decrease in sorafenib activity. Mechanistically,  $\alpha$ v $\beta$ 3 integrin is activated by osteopontin and stimulates the PI3K/Akt/GSK3 pathway [22]. In hepatocellular carcinoma, galectin-1, a  $\beta$ -galactoside-binding protein, is a negative prognostic factor [136], whose expression increases sorafenib resistance [23]. Galectin-1 stimulates  $\alpha$ v $\beta$ 3 expression and hyperactivation of the  $\beta$ 3/FAK/PI3K/Akt pathway to potentiate EMT, but a clear demonstration of a role of  $\beta$ 3 in resistance to sorafenib is missing in this study [23]. Galectin-1 has been shown to interact with other integrins, including  $\beta$ 1 [136–138]. Thus, given their ability to regulate both  $\beta$ 1 and  $\beta$ 3 integrin function, dysregulation of galectin-1 and galectin-3 expression in the tumor microenvironment may have a profound impact on the efficacy of therapies targeting RTKs.

In vitro and vivo data revealed that  $\alpha$ v $\beta$ 3 integrin may support resistance to therapies targeting several RTKs (EGFR, IGFR, PDGFR, FGFR, VEGFR). Furthermore, mechanisms of resistance to EGFR and IGFR TKIs have been identified and found to be independent of  $\alpha$ v $\beta$ 3 binding to ECM ligands, via recognition of the RGD sequence [19,21]. Given the clinical failure of cilengitide to improve the outcomes of cetuximab-treated patients [122,123], the time may have come for the development and use of integrin-targeted drugs that do not target integrin binding to ECM proteins such as RGD-derived peptide.

#### 4. $\alpha$ 6 $\beta$ 4 Integrins

As a nucleator of hemidesmosomes,  $\alpha$ 6 $\beta$ 4 integrin, a laminin-332 (also named laminin-5) receptor, is a master regulator of epithelium integrity and homeostasis. Hemidesmosomes are junctional structures that mediate the firm adhesion of epithelial cells to the basement membrane by linking intermediate filaments to laminin-332. Dysregulation of  $\alpha$ 6 $\beta$ 4 leads to aberrant hemidesmosomal and epithelial dysfunction [139,140]. It has been reported that hemidesmosomal  $\alpha$ 6 $\beta$ 4 integrin is not fully competent for signal transduction, suggesting that epithelium/basement membrane attachment remains its main function in healthy tissue [24,141].

##### 4.1. Crosstalk between $\alpha$ 6 $\beta$ 4 Integrin and Growth Factor Receptors

Hemidesmosomes are dynamic adhesive structures that must be dismantled to allow epithelial cell migration during wound healing.  $\alpha$ 6 $\beta$ 4 interaction with hemidesmosomal proteins is tightly regulated by EGFR signaling pathways [142–147]. EGFR activation promotes the phosphorylation of serine residues in the signaling domain of  $\beta$ 4, which disrupts its interaction with plectin, a linker between integrin and intermediate filaments. The phosphorylated  $\beta$ 4 cytoplasmic domain serves as a docking platform to stimulate signaling pathways (such as Src, PI3K, Rho GTPases) and synergize with RTKs. The clinical significance and roles of  $\alpha$ 6 $\beta$ 4 in carcinoma development and progression have been extensively reviewed [148,149]. In mice, the ablation of  $\alpha$ 6 integrin in intestinal epithelial cells has led to hemidesmosomal disruption and a loss of epithelial/basement membrane junction integrity. These mice spontaneously developed long-standing colitis and subsequent colorectal carcinoma [150]. This may suggest that  $\alpha$ 6 $\beta$ 4 acts as a tumor suppression gene. However, except in basal carcinoma and prostate carcinoma,  $\alpha$ 6 $\beta$ 4 is overexpressed in epithelial tumors and largely contributes to cancer progression and poor prognosis [148]. In these tumors, over-activation of the EGFR, HER2 or c-Met pathways disrupted plectin/ $\alpha$ 6 $\beta$ 4 integrin coupling and hemidesmosomal disassembly [151,152].  $\alpha$ 6 $\beta$ 4 becomes

fully competent for signal transduction and cooperation with RTKs [24,153], and can promote cancer cell proliferation and survival, tumor invasion, metastasis and angiogenesis [149].

#### 4.2. $\alpha 6\beta 4$ Integrin and Resistance to Anti-HER2 Therapies

Although  $\alpha 6\beta 4$  integrin is a pertinent therapeutic target in most forms of carcinoma, few studies have evaluated its potential to trigger RTK-targeted therapy resistance. Using an in vitro knock-in system, Guo and colleagues established a murine model in which endogenous  $\beta 4$  integrin was replaced by signaling-defective  $\beta 4$  integrin (lacking the carboxyterminal moiety of its intracellular domain) in the mammary gland of MMTV-Neu(YD) mice [24]. In this model, wild-type (WT)  $\beta 4$  integrin, but not the mutant form, synergized with HER2 to increase mammary carcinoma tumorigenicity. Interestingly, the therapeutic activity of gefitinib was dampened in WT- $\beta 4$  mice compared to mutant- $\beta 4$  mice, indicating that  $\beta 4$  signaling function can promote resistance to anti-HER2 drugs. The molecular pathway eliciting this resistance is independent of HER2 phosphorylation and remains unknown. Small molecules or antibodies capable of disrupting the integrin/HER2 heterocomplex may improve HER2-targeted therapies. In human breast cancer cells, the expression of laminin-332 or  $\alpha 6\beta 4$  integrin triggers a notable resistance to trastuzumab and lapatinib [25]. Gefitinib-mediated cell toxicity was substantially reduced when hepatocarcinoma cells were exposed to laminin-332 but not to other ECM proteins such as collagen or fibronectin [27]. More recently, high  $\beta 4$  integrin expression was associated with a gefitinib-resistant phenotype in gastric cancer cells [26]. The resistant phenotype could be reverted by RNA-mediated  $\beta 4$  silencing, whereas sensitive cells became more resistant to gefitinib after  $\beta 4$  overexpression. A clinical study in 38 patients has indicated some correlation between  $\beta 4$  expression and gefitinib resistance. However, given the small sample size, it is far too early to draw any conclusion about the potential repercussions of this observation [26]. Another clinical study showed that  $\beta 4$  integrin polymorphism expression was associated with resistance to therapy. The authors examined the expression level of three different  $\beta 4$  polymorphisms in HER3-negative/KRAS WT metastatic colorectal cancer from patients receiving irinotecan/cetuximab. Although conducted in a small cohort of patients, the study showed a significant decrease in progression-free survival and overall survival in patients harboring the  $\beta 4$  rs8669 G polymorphism [154].

It is clear that  $\alpha 6\beta 4$  can unleash the oncogenic potency of RTKs in cancer cells. Data obtained from cell lines, murine models and patient samples are the first insight into the role of  $\alpha 6\beta 4$  integrin in resistance mechanisms to TKIs and antibodies against members of the HER family. Further investigation is required to assess the clinical relevance of these observations. Targeting  $\alpha 6\beta 4$  integrin/RTK interaction could be a promising strategy for overcoming resistance. Another strategy could be to use integrin  $\beta 4$  expression and polymorphism to stratify patients to EGFR-targeted therapies.

## 5. Integrins and Carcinoma-Associated Fibroblasts

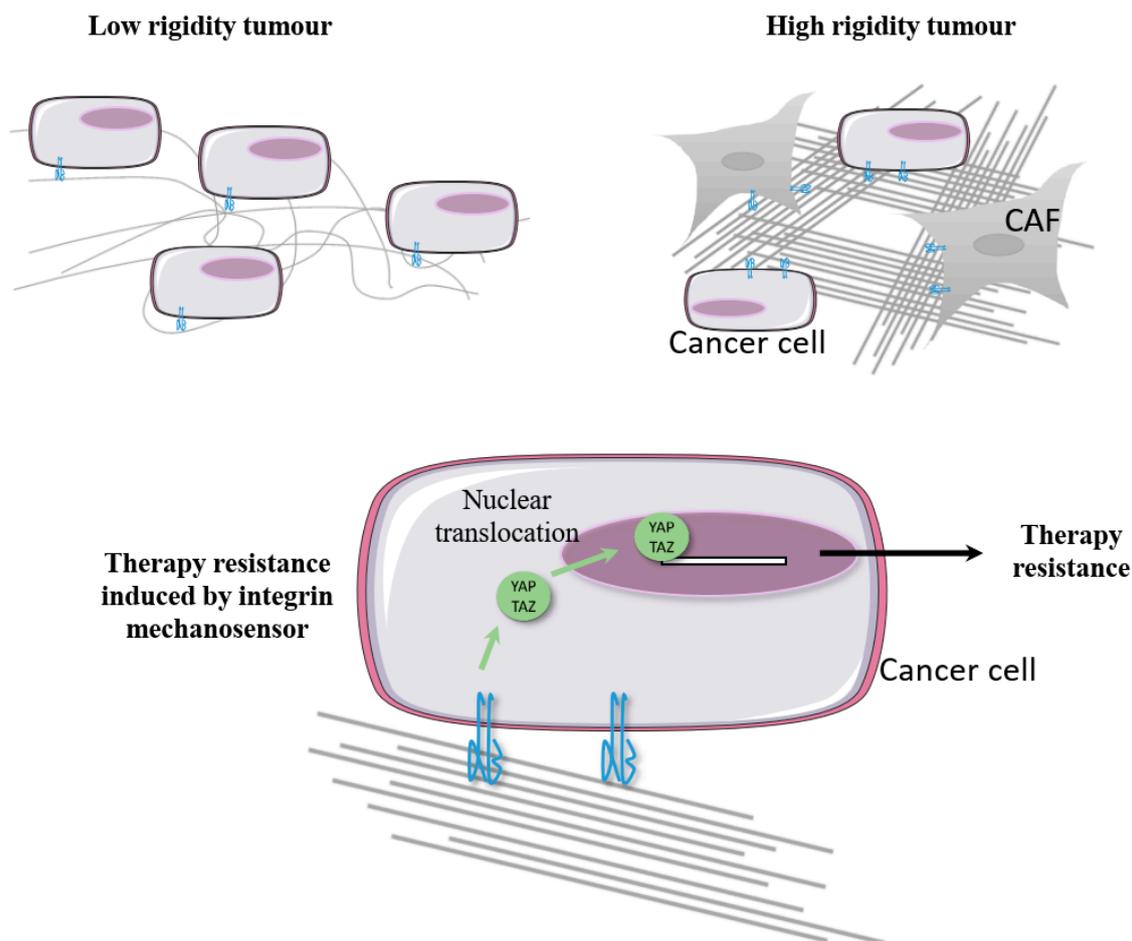
Tumor progression relies on close interaction and communication between cancer cells and cancer-associated fibroblasts (CAFs) through several mechanisms, including paracrine signals (transforming growth factor- $\beta$ , IGF-1, exosomes), cell-to-cell contact and ECM remodeling [155,156]. Emerging data indicating that CAFs can decrease therapeutic response (including to anti-RTK drugs) have been extensively reviewed [157]. We will restrict our analysis to research incriminating integrin involvement in CAF-mediated therapy resistance.

In breast cancer cells, physical interaction between cancer cells and stromal cells (mesenchymal stem cells or CAFs) strongly protects against lapatinib or trastuzumab [158,159]. In those two studies, no experimental data could attest to any role for integrin in CAF-mediated resistance. However, CAF/breast cancer cell interaction requires the synthesis of hyaluronic acid by CAFs [159]. Hyaluronic acid can bind to and activate CD44, a known partner and regulator of integrins [160]. Alternatively, integrin may also be involved in CAF/cancer cell interaction. For instance, we showed that  $\alpha 5\beta 1$  integrin can promote cell/cell interaction during tumor spheroid formation [161]. This particular

integrin can mediate CAF interaction with a highly aggressive subset of ovarian carcinoma cells. Heterotypic CAF/cancer cell spheroids promote the metastasis of ovarian cells in mice [162].

In vitro assays have revealed that collagen fiber synthesis and assembly by CAFs promote lung cancer cell resistance to gefitinib and osimertinib [163]. Another study showed that collagen-mediated resistance to TKIs requires the activation of the Akt/mTOR pathway [164]. Interestingly, the inhibition of collagen synthesis or  $\beta 1$  integrin function suppresses this resistance, offering new therapeutic options [163]. These observations may be clinically relevant as increased collagen deposition has been observed in erlotinib-resistant xenografts [163], and as progression-free survival has been seen to decrease in gefitinib-treated patients with collagen-rich lung tumors [164]. Another group used genetically modified mice expressing inducible RAF-driven tumors to model melanoma development in the ear. For the longitudinal monitoring of tumor development, the authors used intravital two-photon microscopy of fluorescently tagged melanoma cells. Upon MEK inhibition, the tumors transiently responded but returned to their original size after 12 weeks of treatment. It was noted that the cells that survived MEK inhibition co-localized with collagen bundles (imaged by second harmonic generation) [165].

Hirata and colleagues have shown that melanoma-associated fibroblasts can drive resistance to the BRAF (v-Raf murine sarcoma viral oncogene homolog B) inhibitor vemurafenib by stimulating fibronectin production and remodeling, and subsequently promoting  $\beta 1$ /Src/FAK pathway signaling in melanoma [166]. Another study confirmed the crucial role of fibronectin/ $\beta 1$  integrin signaling in melanoma adaptation to BRAF inhibition [167]. In both studies, following vemurafenib treatment, increases in fibrous ECM were observed in xenograft tumors and in several excised human melanomas. The concomitant inhibition of BRAF and FAK to suppress PDX growth in mice has been advanced as one way of improving therapy [166]. The efficacy of this therapeutic option was recently confirmed through the screening of a kinase inhibitor library [168]. Matrix stiffening generates mechanical forces that are transduced through the plasma membrane by integrin adhesion and stimulate YAP and TAZ (transcriptional coactivator with PDZ-binding motif) nuclear translocation and activation [169,170]. Cancer cells that express the activating mutant of Ras (RASG12D) are addicted to this oncogene. Studies from two different laboratories conjointly established that YAP and TAZ activation drive mutant KRAS-independent tumor growth and progression [171,172]. Therefore, increased matrix stiffness is sufficient to protect BRAF-mutant melanoma cells from BRAF inhibition [166], while YAP/TAZ activation induces resistance to therapy targeting the RAS/RAF pathway [173,174]. Additionally, several concurrent reports confirmed that matrix stiffening modulates cancer cell response to TKIs [175–177]. As mechanotransducers, integrin and FAK play key functions in tension generation by CAFs [178–182]. In turn, ECM stiffening enhances integrin signaling in cancer cells [183] and contributes to cancer progression [184]. Hence integrin mechanosensing plays multiple roles in the microenvironment (both in stromal and cancer cells) that promote tumor growth and therapy resistance [185,186]. It can be hypothesized that YAP/TAZ regulation by integrin mechanotransduction provides a safe haven that protects cells from therapies targeting the RTK pathway (Figure 4).



**Figure 4.** Hypothetic model showing how integrins may trigger therapy resistance in stiff micro-environmental niches. Therapy-resistant tumors are often characterized by an increase in matrix stiffness. Cancer-associated fibroblast (CAF) integrins (mainly  $\alpha 5\beta 1$  integrin) generate mechanical forces that increase ECM protein assembly and matrix rigidity. In cancer cells, the sensing of CAF-generated tension by integrins activates transcriptional co-regulators YAP and TAZ and their translocation to the nucleus. The transcriptional response leads to therapy resistance (adapted from [186]).

## 6. Conclusions

As shown in this review, integrin interacts with several RTKs such as the HER family, c-Met, PDGFR and others. These interactions can give cells an intrinsic ability to better adapt to and resist targeted therapies. Several integrin inhibitors were described and are being tested in clinical settings, albeit with no strong benefit, not even in combination with RTK inhibitors. It should be noted that, although in clinical practice integrin-targeted therapies are based on the inhibition of their adhesive function by small antagonist molecules or monoclonal antibodies, several studies have shown that integrin/RTK interactions and integrin-mediated resistance to therapies targeting RTK can be elicited by unbound integrins [19,95,115,153]. The ability of integrins to form functional molecular complexes with RTKs makes the situation much more difficult to understand. But it also makes new treatment approaches possible, be it predicting the efficacy of anti-RTK therapies in subpopulations of patients based on their level of heterocomplex expression [18,59] or developing treatments for disrupting integrin/RTK complex formation [17,18]. Aptamers, small nucleic acids used in treatment [187], can disrupt EGFR/ $\beta 3$  integrin interaction to inhibit tumor growth [188]. Meanwhile, targeting EGFR/uPAR using an integrin antagonist confers sensitivity to vemurafenib [189]. Finally, Kim and colleagues created an antibody that co-targets EGFR and neuropilin-1, a receptor that physically interacts with active  $\beta 1$  integrin. This antibody enhanced  $\beta 1$  integrin internalization and so led to the inhibition of  $\beta 1$  signaling,

reducing tumor volume in in vivo experiments [11]. All these examples illustrate the strong potential of this new therapeutic concept.

New functions of integrins are continually being discovered, proving their importance in therapy resistance. A better understanding of the molecular mechanisms underlying the integrin/RTK relationship could one day make it possible to improve the efficacy of therapies targeting RTKs.

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