*Review*

# Collagen Remodeling along Cancer Progression Providing a Novel Opportunity for Cancer Diagnosis and Treatment

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**Abstract:** The extracellular matrix (ECM) is a significant factor in cancer progression. Collagens, as the main component of the ECM, are greatly remodeled alongside cancer development. More and more studies have confirmed that collagens changed from a barrier to providing assistance in cancer development. In this course, collagens cause remodeling alongside cancer progression, which in turn, promotes cancer development. The interaction between collagens and tumor cells is complex with biochemical and mechanical signals intervention through activating diverse signal pathways. As the mechanism gradually clears, it becomes a new target to find opportunities to diagnose and treat cancer. In this review, we investigated the process of collagen remodeling in cancer progression and discussed the interaction between collagens and cancer cells. Several typical effects associated with collagens were highlighted in the review, such as fibrillation in precancerous lesions, enhancing ECM stiffness, promoting angiogenesis, and guiding invasion. Then, the values of cancer diagnosis and prognosis were focused on. It is worth noting that several generated fragments in serum were reported to be able to be biomarkers for cancer diagnosis and prognosis, which is beneficial for clinic detection. At a glance, a variety of reported biomarkers were summarized. Many collagen-associated targets and drugs have been reported for cancer treatment in recent years. The new targets and related drugs were discussed in the review. The mass data were collected and classified by mechanism. Overall, the interaction of collagens and tumor cells is complicated, in which the mechanisms are not completely clear. A lot of collagen-associated biomarkers are excavated for cancer diagnosis. However, new therapeutic targets and related drugs are almost in clinical trials, with merely a few in clinical applications. So, more efforts are needed in collagens-associated studies and drug development for cancer research and treatment.

**Keywords:** cancer; the extracellular matrix (ECM); collagen remodeling; interaction; mechanism; diagnosis; biomarker; therapeutic target; treatment

## 1. Introduction

Cancer is a serious disease for humans with high morbidity and death. The extracellular matrix (ECM) is a non-ignored factor in cancer progression due to the fact that it is the major component of tumor stroma, playing the roles of the physical scaffold and regulator of cell and tissue function. ECM could not only act as a medium to conduct signals but also elicits biochemical and biophysical signaling to excite cells [1,2]. The interaction between tumor cells and ECM is bidirectional and dynamical, which could reshape the morphology of perimalignant tissue continuously. Recent studies have shown that tumors could directly leverage ECM remodeling to create a microenvironment that promotes tumorigenesis and metastasis. Conversely, many cell behaviors are inspired by transformed ECM, such as adhesion, migration, angiogenesis, and canceration [3,4].

In the complex interaction between ECM and tumor cells, collagens play a significant role involved in multiple actions. Collagens are the major component in ECM, which constitute up to 30%—28 different collagens have been identified. Multiple subtype collagens participate in the construction of both matrices of ECM, i.e., base-membrane and interstitial matrix, and create special ECM compositions in different tissues [5,6]. Recently, many studies reported the abnormal appearance in the cancer progression, including degradation, remodeling, fragmentation settlement, linearization, and fasciculation. It is confirmed that collagens are relevant to the precancerous lesion and cancer progression. Based on the mechanisms of collagens involved in the multiple stages of cancer progression, the value of diagnosis and prognosis is developed. Moreover, it provides opportunities to identify new therapeutic targets for cancer treatment. This review investigated the complex response of collagens in cancer progression and summarized the interaction between collagens and cancer cells. Then, we focused on the diagnosis value of collagen-associated imaging and biomarkers. Finally, we discussed the therapeutic opportunities of targeting collagens for cancer treatment.

## 2. Collagen Is a Significant Concern for Cancer Research Associated with the ECM

### 2.1. Collagens Are the Major Component of ECM

Collagens are a superfamily comprising 28 members characterized by collagen α chains [6,7]. According to the supramolecular organization, collagens are divided into fibrillar collagens and non-fibrillar collagens. Fibrillar collagens occupy 90% of the totality, including types I, II, III, V, XI, XXIV, and XXVII. They show elongated, rod, or banded fibril structures under electron microscopy. In comparison, others are non-fibrillar collagens, which form other types of supramolecular structures. Non-fibrillar collagens are further subdivided into fibril-associated collagens with interrupted triple helices (types of IX, XII, XIV, XVI, XIX, XX, XXI, and XXII), network-forming collagens (types IV, VI, VIII, and X), beaded filament-forming collagens (types VI, XXVI, and XXVIII), anchoring fibrils (type VII) and transmembrane collagens (types XIII, XVII, XXIII, and XXV). Collagens participate in the formation of both forms of ECM, i.e., the base-membrane and interstitial matrix. Fibrillar collagens have a clear structural role of mechanical support and dimensional stability, which could provide three-dimensional frameworks for tissue and organs. As an example, type I collagen, as fibrillar collagen, is the main protein in skin, contributing to the tensile strength of skin [6,8]. Non-fibrillar collagens are also essential to maintain tissue structure; for instance, the type IV collagen network is the main scaffold structure of the base membrane. In addition, non-fibrillar collagens are the key regulators to anchor and organize the ECM meshwork. It has been reported that an anchoring bridge is created between the base membrane and the interstitial matrix by the regulation of type VI collagen [9].

### 2.2. The Observation Methods of Collagens in Research and Clinic

The paramorphia of collagens is a significant signal of many diseases, especially fibrosis and precancerosis. Several imaging modalities were developed for quantitative or qualitative analysis collagens. The coarse collagen fiber could be observed directly under the light field of optical microscopy, the visual scenes of which are shown in Figure 1A. However, the tiny collagen fibrils or soft networks are hard to be identified under optical microscopy. Pathological staining technology offers the assistance to catch high-recognition images under light fields, especially for clinicopathological sections. Of note, immunohistochemistry (IHC) could recognize the types of collagens with the assistance of optical microscopy. Fluorescence immunostaining is a method to mark the collagens with a fluorescence dye, then the marked collagens are highlighted under the excitation light of a fluorescence microscope from the background. This method is suitable for all subtypes of collagens, whether fibrous or not; however, this method is hard to apply in practical applications due to the fact that the fluorescence dye is hard to wash completely from the dense networks, causing significant interference to collagen identification. Collagen fiber is a non-centrosymmetry and high second-order nonlinear coefficient structure that could

produce the signal of second-harmonic generation (SHG) under two-photon excitation. This provides an excellent opportunity to image collagens, and SHG imaging has been promoted to be a popular and effective approach to investigate collagens in the laboratory. As an example, SHG imaging is developed to investigate collagen fiber organization, which has a high resolution capable of recognizing faint signals [10]. In fact, SHG imaging of collagens is always used combining with confocal microscopy, which could catch the interior signals of the samples to reconstruct 3D images [11,12]. We took an SHG image of type I collagen fibers in an in vitro experiment using confocal microscopy shown in Figure 1B. Due to the fibrous structure differs from other matrices, the pure reflective mode of the confocal microscope is available to take the fiber signal, although the clarity is worse in contrast to SHG imaging [13–15]. Figure 1C exhibited the collagen network structure in an in vitro experiment using the reflective mode of the confocal microscope. Electron microscopy is an instrument manufactured by the principle of electron photons, which replaces light beams and optical lenses with electron beams and electron lenses to take the subtle structure imaged with a very high magnification. Fortunately, collagen fibers could be imaged by the two commonly types of electron microscopy, i.e., scanning electron microscopy (SEM) and transmission electron microscopy (TEM) [16–18]. SEM could see the morphology of collagens limited to surface and longitudinal. We took the porous structure by SEM, shown in Figure 1D. TEM could evaluate the cross sections through 3D imaging. Figure 1E is the structure of collagen type I under TEM. Cryo-TEM advanced the TEM technique allowing the sample examined to maintain the frozen-hydrated state and removing the step of heavy-metal staining. The early banding analysis of reconstituted collagen fibrils was performed from cryo-TEM images [19–21]. Atomic force microscopy (AFM) is another morphology detection instrument based on a completely different principle, i.e., van der Waals force. AFM could be used to confirm the inner assembly of collagen fibrils. As an example, Figure 1F exhibited the microstructure of a single collagen fibril in a high magnification AFM image. However, AFM could only scan the 3D topographic feature, but not the section structure inside the matrix [22–24].
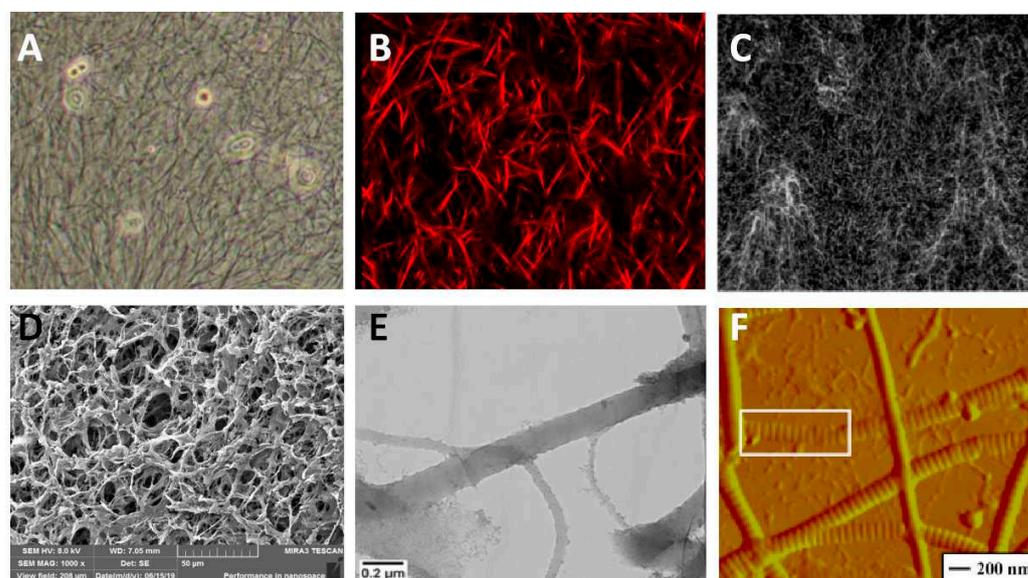


**Figure 1.** Several examples of collagen detecting methods. (**A**) light field of optical microscopy. (**B**) SHG imaging. (**C**) The reflection mode of confocal microscopy. Reprinted/adapted with permission from Ref. [3]. (**D**) SEM imaging. (**E**) TEM imaging. Reprinted/adapted with permission from Ref. [6]. (**F**) AFM imaging. Reprinted/adapted with permission from Ref. [12].

Clinically, medical imaging technology is an important contribution to disease diagnosis and surgical guidance, which is popular due to its non-invasive, including ultrasound, X-ray, computed tomography (CT), and nuclear magnetic resonance imaging (MRI). The

medical imaging technology allows the sample to be examined in a close to physiological hydration state without chemical fixation of sectioning. Diffraction pattern signals are inspired by high-intensity X-rays scattering from the arranged collagen molecules and fibrils in the bulk matrix. So, X-ray is available to analysis the average diameter, lateral arrangement, and alignment of collagen fibrils; as an example, corneal ultrastructure is obtained by X-ray with a powerful synchrotron source [25,26]. CT and MRI are able to analyze the collagen fibers quantitatively. Karjalainen et al. used micro-computed tomography to analyze the three-dimensional collagen orientation of the human meniscus posterior horn in health and osteoarthritis [27]. Eder et al. used MRI to evaluate the regional collagen fiber network in the human temporomandibular joint disc [28]. Ultrasound is developed to assess collagen microstructure based on the integrated backscatter coefficient (IBC). Mercado, Karla P. et al. employed IBC as a quantitative ultrasound parameter to detect the quantify spatial variations of collagen fiber density and diameter [29]. Kenton et al. prospectively characterize the collagen organization in the Achilles and patellar tendon [30]. However, IHC still plays an irreplaceable role in the clinic due to its ability to recognize the types of collagens. Pathological detection based on IHC is the gold standard for tumor diagnosis in the clinic.

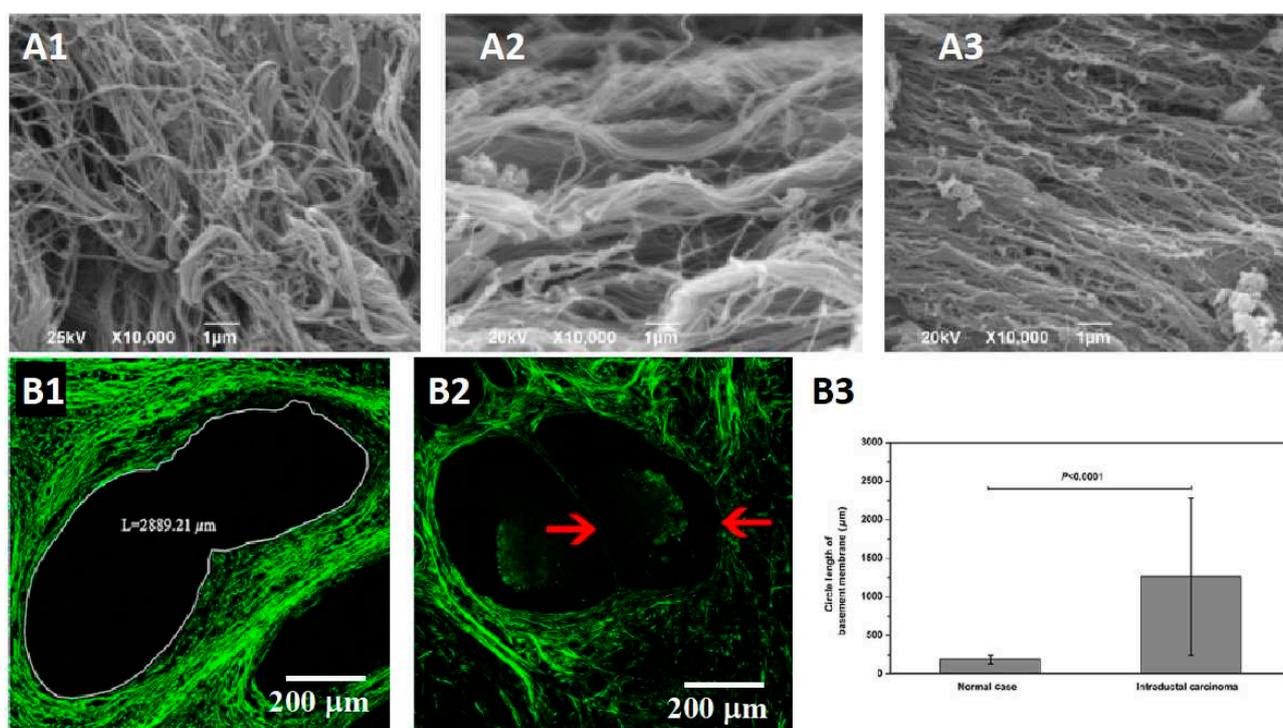## 3. Collagen Remodeling Is a Significant Signal in Cancer Progression

### 3.1. Precancerous Lesions

Stromal alterations are the reference precursors to predict the progression of carcinoma, especially collagens, which is the main component of the ECM. The occurrence of fibrosis and the base membrane abnormality, which are mainly involved by collagens, are the important cues orienting to deterioration, having a significant clinical meaning. In precancerous lesions, it is likely to occur due to the abnormal ratio of collagen types, new collagen types secreted, and abnormal molecular structure, causing the abnormal ECM.

The fibrosis of organ tissue is an important cue to draw attention to, which is likely to be a stage of deterioration, such as liver fibrosis, lung fibrosis, oral submucosa fibrosis, and so on. Most hepatocellular carcinoma develops through the progression of chronic liver injury, hepatic inflammation, and fibrosis, so liver fibrosis is a precursor of cancerization. It has been confirmed that high fibrosis index is positively correlated with the risk of hepatocellular carcinoma [31,32]. The configuration of collagen types is changed greatly in the progression of fibrillation. In normal liver, the collagens in ECM are type IV and VI, which are non-fibrillar; however, a great accumulation of fibrillar collagens occurs in the fibrotic liver, such as collagen type I and III [33]. Similarly, idiopathic pulmonary fibrosis is considered to have a high risk of concomitant lung cancer in the clinic. What is worse, patients with idiopathic pulmonary fibrosis have a poor prognosis with a 2–5 year survival time, which is worse than liver fibrosis [34]. Enhancing nodules in post-radiation fibrosis in CT imaging could be an early detecting method of recurrent lung cancer [35]. The deposition of collagens in the interstitium is the direct reason for fibrosis. In early pulmonary fibrosis, collagen type III predominates in the matrix; however, the proportion is gradually replaced by collagen type I along the process of pulmonary fibrosis to the late stage [36]. Oral submucous fibrosis is a precancerous disorder and has a 1.5–15% chance of transforming into a malignant tumor. The characteristics of oral submucous fibrosis are abnormal collagen deposition. In oral submucous fibrosis cells, the collagen synthesis is increased and the ratio of the $\alpha 1(I)$ to $\alpha 2(I)$ chains of type I collagen is ~3:1 whereas ~2:1 in normal cells [37,38].

The analysis of collagen fibers is significant in predicting cancer. Despotovic et al. caught the SEM images of the perimalignant tissue shown in Figure 2A. They found that the altered organization of collagen fibers was observed at 10 cm and 20 cm away from the malignant tumor. The alignment of collagen fibers is step increased as proximity to the tumor [39]. Wu et al. focused on the base membrane in intraductal carcinoma, a precancerous lesion of invasive ductal carcinoma. They found that the base membrane was distorted and elongated compared with the normal cases (Figure 2B). Several types

of gynecological cancers are reported differently in terms of precancerous lesions, such as breast cancer, ovarian cancer, and vulvar cancer. Castor et al. characterized the collagen fibers in preneoplastic lesions compared with normal tissue and squamous carcinoma in vulvar cancer using SHG microscopy. They found that the collagen fibers showed better organization in the normal tissue than in the other two stages. The devise parameters of collagen fibers showed reducing in squamous carcinoma and preneoplastic lesions compared with normal tissue, i.e., quantity, organization, and uniformity; however, no obvious difference was observed between squamous carcinoma and preneoplastic lesions [40]. In cervical precancers, several collagen-associated indicators directly affect the quantitative classification of precancerous stages, including the density and degree of linear arrangement, collagen degradation, and the breakage of collagen cross-links. Zaffar et al. focused on this valuable information by developing a series of studies of the spatial frequencies of collagens for cervical precancer detection [41,42]. The expression of collage IV seriously affects the integrity of the base membrane because collagen IV is the main complement of the base membrane. As a precancerous lesion of squamous cell carcinoma in malignant skin tumors, actinic keratosis has shown the premonition of collagen IV low expression. Hirakawa et al. compared the expression of collagen IV using immunohistochemical in actinic keratosis tissue. The result showed that collagen IV in dysplastic areas of actinic keratosis samples was lower than peri-lesional tissue and no longer continuous [43].



**Figure 2.** Collagen remodeling in precancerous lesions is a signal of cancerization. (**A1–A3**) The SEM images of collagen fibers in the health tissue and 10 cm and 20 cm away from the malignant tumor [39] (**A1**) The collagen fibers in the health tissue are thin collagen fibers forming a dense network. (**A2**) The collagen fibers at 20 cm away from the tumor, thick and aligned. (**A3**) The collagen fibers at 10 cm away from the tumor, highly aligned. (**B1–B3**) The difference of base membrane in intraductal carcinoma, a precancerous lesion of invasive ductal carcinoma [44] (**B1**) The base membrane shows a distorted structure with a larger size. (**B2**) The base membrane is destroyed in the evolution from intraductal carcinoma to invasive ductal carcinoma. (**B3**) The statistics data of the circle length of base membrane. The circle length is elongated observably in precancerous lesions compared with normal cases.

### 3.2. Post-Cancerous

### 3.2.1. Breaching Base Membrane

In the development of cancer progression, collagens become from a passive barrier resisting cancer cells to an accomplice in promoting the progression. The base membrane is a baffle between tumor cells and normal tissue originally; however, it would be breached at the early stage of carcinogenesis. The main reason is collagen IV, which occupies the major complement of the base membrane, is degraded directly or indirectly by tumor cells. In the degrading progress, matrix metalloproteinase plays an indispensable role, which is secreted by tumor cells or stimulated epithelial or stromal cells. In the subsequent progression of cancer development, degrading collagens remains an effective strategy to create roads to invasion or migration. Yan et al. reported a period that collagens exhibited a significant loss in invasive ductal carcinoma compared to the normal case and precursor lesion [44]. Recently, another cue is revealed that cancer cells could break the base membrane just facilitated by physical forces, which is a completely different manner independent of protease. As evidence, the collagen IV meshwork exhibits a densified structure at the adjacent disruption; on the contrary, the collagen IV scaffold should be decreased under the degradation theory. Piercing filopodia is captured in further studies, which is proved to have a pivotal role in the mechanical response model. The force of push and pull by the contractility of piercing filopodia is considered an explanation of the base membrane non-protease disruption [45–47].

### 3.2.2. Enhancing ECM Stiffness

Enhancing the stiffness of ECM is another strategy to promote tumor cell migration and invasion through the pathway of activating integrins to increase the adhesion between cells and substrate. Castor et al. found that the parameters of collagen fibers present higher in metastatic vulvar cancer patients than in that without metastases [40]. High ECM stiffness is mainly realized by increasing the secretion of fibrous collagens and the deposition of non-fibrous collagens, most notably collagen type I and type IV [48,49]. In medical statistics, ECM stiffness is considered a reason for tumor rise incidence with aging because it is a fact that the aged tissues are stiffer due to containing more aberrant cross-linked collagens [50]. High collagen density in tumors is often closely correlated with poor prognosis; however, the association between collagen density and cancer progression is not completely clear. Recent reports studied it from various perspectives. The most accepted view is that ECM stiffness is closely related to cancer-associated fibroblasts (CAFs) [51–54]. This viewpoint is supported because CAFs are the main producer of abnormal collagen fibers. Shibata et al. reported that CAFs promote ECM stiffness in response to the signals from yes-associated protein 1 (YAP1) [55]. However, Farhat et al. found that abnormal activation and expression of the Lox family of proteins, a group of extracellular enzymes catalyzing the cross-linking of collagens, would lead to the ECM toward increased rigidity and fibrosis [56].

### 3.2.3. Orienting the Collagen Fibers

Orienting the collagen fibers is a significant manner of remodeling the ECM by cancer cells. The stress of tumor growth remodels the collagen fibers toward the tumor circumference at the tumor periphery. Those oriented collagen fibers provide a highway to cancer cell invasion directly [57–60]. Meanwhile, the tension of aligned collagen fiber bunches contributes to ECM stiffness [61]. Many studies reported the high orientation of collagen fibers in the tumor location [13,57,59,62]. The mechanism of collagen fibers orientation in the malignant tumor is still unclear. Many scientists dedicated themselves to this study, and they revealed it is a complex process, maybe participated in by tumor cells, CAFs, mesenchymal cells, and interstitial fluid. Tumor cells remodel the collagen fibers through various manners, including the stress of tumor growth, the pseudopod with contractility, the protease, and so on, which is a complex process with multiple pathways [61,63–67]. The examples are shown below. Ray et al. reported that the traction forces from the di-

rected migration of cancer cell clusters are a mechanism of collagen fiber alignment [68]. Drifka et al., using a pancreatic ductal adenocarcinoma model, found that human pancreatic stellate cells could orchestrate the alignment of collagen fibers, and they further found that the aligned collagen fibers, in turn, enhanced cancer cell migration. Bayer et al. showed that the collagen receptor DDR2 in CAFs reorganizes collagen fibers at the tumor-stromal boundary [69]. Hanley et al. reported that CAFs could induce the formation of elongated collagen fibers [70]. Del Amo et al. constructed a collagen-based osteoblasts model in 3D microfluidic devices, and the data suggested that a high rate of interstitial fluid flow could modify the orientation of collagen fibers [71].

## 4. Remodeled Collagens Assist Cancer Progression

### 4.1. Promoting Angiogenesis

In cancer progression, limited oxygen and nutrients are always insufficient for the rapid growth of cancer cells. Angiogenesis is induced under a poor supply of oxygen and nutrient. The angiogenesis process is always accompanied by the upregulation of collagens and ECM-modifying enzymes, which has been confirmed in different human tumor types. That is because the collagen network provides the scaffold for recruited endothelial cells migrating during angiogenesis. Even the remote collagen fiber network is induced by tumor cells into orientation steers for angiogenesis. We illustrated the process of angiogenesis induced by collagen fibers in Figure 3A. Piotrowski-Daspit et al. took a confocal image of a representative tissue comprised of breast cancer cell MDA-MB-231. They found that the collagen fibers showed high alignment obviously (Figure 3B). The collagen network provides the intact physical connection with tumor tissue for vascular endothelial cells' mechanical sensing, which is considered essential during angiogenesis [72]. Nathaniel et al. observed the fibril organization around angiogenic sprouts and growing neo-vessels in real time. They found that a strong association of fibrillar collagens occurred during vessel reconstitution and a substantial collagen fibril reorganization at the sites of sprout and neo-vessel tips [73]. Luthria et al. investigated the vasculature around the tumor in the dense collagen micro-environment—shown in Figure 3C [74]. Niels et al. reported that type VIII collagen was elevated in diseases associated with angiogenesis and vascular remodeling, such as pulmonary fibrosis and cancer [75].
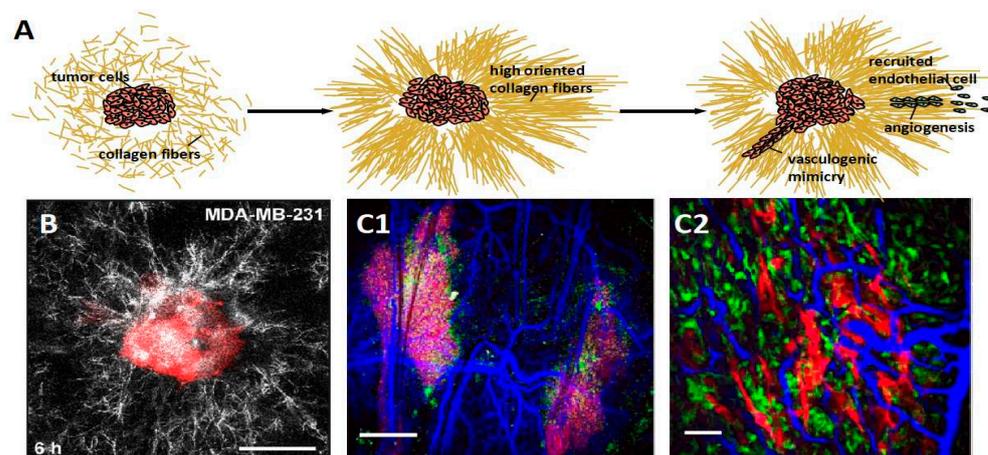


**Figure 3.** Tumor cells organize the disordered collagen fibers into orientation, further providing a scaffold to recruit endothelial cells (green cell in illustration) for angiogenesis or inducing vasculogenic mimicry constituted by tumor cells (red cell in illustration) without endothelial cells presenting. (**A**) The cartoon diagram displays the process of angiogenesis. (**B**) A confocal image of a representative tissue comprised of breast cancer cell MDA-MB-231. The collagen fibers around the tissue are aligned, obviously. Reprinted/adapted with permission from Ref. [76]. (**C1,C2**) The SHG images show the vasculature (blue) formed neighbor tumor within the micro-environment of high dense collagen matrix. Reprinted/adapted with permission from Ref. [74].

Another vasculature-like structure could also support tumors with blood, which is called vasculogenic mimicry constructed by cancer cells without endothelial cells. The primary trigger is dense collagen, inducing cancer cells to form interconnected networks [4]. Velez et al. found that the collagen matrixes with small pores and short fibers induced vasculogenic mimicry. The upregulation of β1-integrin is triggered by the collagen matrix architecture and is considered a significant reason in the follow-up research [77]. The non-fibril collagens contribute to vasculogenic mimicry, such as collagen type IV, VI, and XVI. Bedal et al. found the NC11 domain of human collagen XVI, one non-fibril collagen, induced vasculogenic mimicry in oral squamous cell carcinoma cells. The process is realized by triggering the generation of tubular-like net structures on a laminin-rich matrix [78].

### 4.2. Promoting Invasion

Escaping from the primary site is another strategy employed by cancer cells to obtain supplies; collagens also play a significant role in this process. Collagen fibers induce cancer cell migration by contact guidance [68]. Especially, the aligned collagen fibers are confirmed to provide "a highway" to cancer cell invasion [79–81]. The guidance of collagen fibers runs through the major process of cancer progression. In the early stage, the collagen fibers that are perpendicular to the solid tumor provide conduits to escape and penetrate the base membrane [58,82]. In the following process, the interface between the collagen fiber bundle in ECM and the peripheral interstitial components provides the opportunity for breakthrough for tumor cells. We illustrated the intravasation guided by collagen fibers in Figure 4A. The role of the "highway" has been verified by several reports. In an experiment on the orientation of collagen fibers, cancer cells could break through the high density of Matrigel along with the collagen fibers, while they were unable to do that in the absence of oriented collagen fibers—shown in Figure 4B [59]. In the process of intravasation (cancer cell entering blood vessel) and extravasation (cancer cell exuding blood vessel), collagen fibers as important participators are remodeled firstly and, in turn, guide the cancer cell invasion [83–86]. Moreover, the orientation and the deposition of collagens make the matrix stiff. The stiffness of the ECM could induce the enhancement of transforming growth factor-β (TGF-β) to increase the cell adhesion to the substrate, further promoting the migration and invasion of tumor cells. Masoud et al. reported that ECM stiffness could make a bridge in the base membrane through the related pathway of transforming growth factor-β (TGF-β), which contributed to EMT [87]. Figure 4C illustrates the process of EMT induced by the high stiffness ECM. Han et al. displayed a merged image of the SHG signal and light field of the pathological section (Figure 4D). They found that the tumor cells invaded along with the direction of fibers [59]; however, the mechanism of the stiffness ECM acting on tumor cells is complex; there are other pathways being investigated as well. For instance, Anne et al. investigated the immune modulatory properties of collagens in cancer, and they revealed that collagens could affect the function and phenotype of various types of tumor-infiltrating immune cells, such as tumor-associated macrophages and T cells [88]. Yu et al., from the perspective of drug transport, revealed that ECM stiffness was a barrier to drug screening at the tumor site [89].

Non-fibril collagens also participate in the invasion process. Fang et al. reported that collagen type IV occurred a series of changes to provide a proper tumor microenvironment for cancer invasion. In the initial stage, collagen IV presents an irregular sheath in the base membrane, and then it is degraded and accompanied by linear redeposition to form invasion fronts, which would become the escape sites of cancer cells [90]. Zhang et al. reported that collagen XIII could promote invasive tumor growth, enhance the stemness of cancer cells, and induce anoikis resistance [91]. Karagiannis et al. investigated collagen type XII by immunohistochemistry and found that collagen XII was highly expressed in the invasion front of cancer cells [92]. Kumagai et al. found that the intercellular expression of type XVII collagen could promote collective invasion by producing intercellular adhesion sites for contact following [93]. Miyake et al. reported that collagen IV and collagen XIII played a pivotal role in tumor invasion by inducing tumor budding [94].
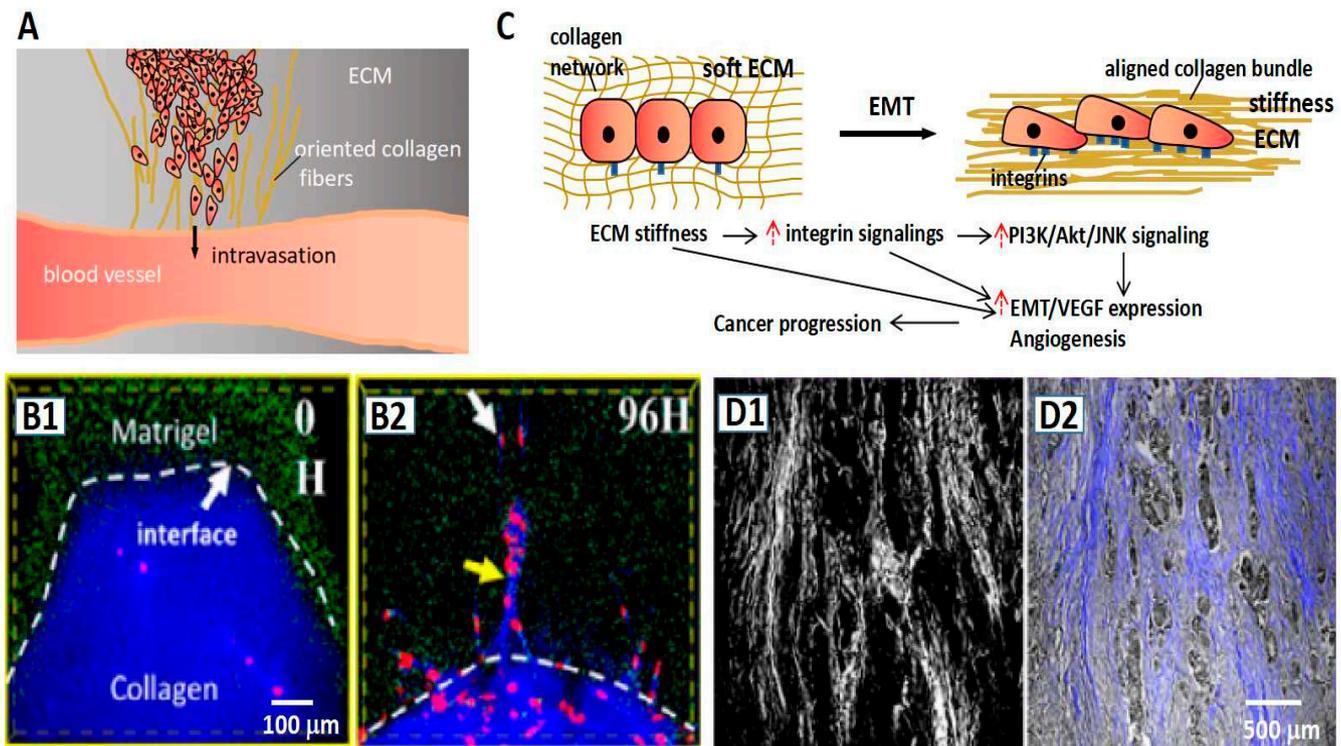
**Figure 4.** Collagens promote cancer invasion. (**A**) The schematic representation of oriented collagen fibers providing a "highway" to guide cancer cells in realizing the intravasation process. (**B1,B2**) The fluorescent images show the stiffness Matrigel (green) region is invaded by cancer cells (red) in the guidance of the oriented collagen fibers (blue) [59]. (**C**) The schematic representation of stiffness ECM inducing EMT accompanied with high adhesion of tumor cells. (**D1,D2**) Tumor cells (gray color in (**D2**)) invade along with the direction of collagen fibers. (**D1**) The SHG signal of collagen fibers in the pathological section. (**D2**) The merge of the light field and SHG signal of the pathological section [59].

## 5. Collagens Provide Opportunities to Cancer Diagnosis and Prognosis

### 5.1. Collagen-Associated Biomarkers for Cancer Diagnosis

Collagens, as the main component of the ECM, would be abnormally expressed or deposited in the location or the pericarcinoma of the cancer site. It is for this reason that collagens are proposed as a diagnostic biomarker in cancer types. Type I collagen is reported to be a good diagnostic marker to detect the metastasis of lung cancer, the expression level of which is a significant indicator of distinct bone involvement happening or not in lung cancer metastasis [95]. The degradation products of type I collagen in serum are a significant reference for diagnosis and prognosis. Nurmenniemi et al. reported that type III collagen N-terminal telopeptide and type I collagen C-terminal telopeptide in serum, which are the degradation products of type I and III collagen, respectively, could be used as a prognostic marker in head and neck squamous cell carcinoma because they are proved closely associated with patient survival [96]. Another report revealed that the levels of matrix metalloproteinase (MMP) generated fragments of type I collagen in serum are valuable as a diagnostic biomarker for lung cancer [97]. The variety of collagens is valuable as a biomarker in the diagnosis of numerous cancers, and we collected and summarized them—we present this in Table 1. Of note, many generated fragments of collagens in serum are available for cancer diagnosis, which provides a convenient detection method through drawing peripheral blood.

**Table 1.** The collagen-associated biomarkers and the applicating cancer types in cancer diagnostic.

| Collagen Type | Biomarker | Cancer Type | Reference |
|---|---|---|---|
| Type I | the expression level of collagen I | bone metastases of lung cancer; bladder cancer; colorectal cancer | [95,98,99] |
| | the carboxyl terminal peptide beta-special sequence, total type I procollagen amino terminal propeptide, alkaline phosphatase of collagen I in serum | bone metastases of lung cancer | [100] |
| | type I collagen C-terminal telopeptide in serum | head and neck squamous cell carcinoma | [96] |
| | MMP-generated fragments of type I collagen in serum | lung cancer; breast cancer | [97,101] |
| | the expression level of collagen type I alpha 1 | hepatocellular carcinogenesis and metastasis | [102] |
| | the carboxyterminal collagen type I telopeptid | breast cancer with bone metastases | [103] |
| | the expression level of collagen type I alpha 2 | gastric cancer | [104] |
| Type III | MMP-generated type III collagen fragment, procollagen type III N-peptide in serum | breast cancer | [101,105] |
| | the propeptide of type III collagen in serum | pancreatic cancer | [106] |
| | the level of procollagen III aminoterminal propeptide | malignant head and neck cancer; cervical carcinoma | [107,108] |
| | procollagen type III N-peptide in serum | gastric cancer; ovarian cancer; lung cancer | [109–111] |
| | type III collagen in serum | hepatocellular carcinoma | [112] |
| | type III collagen in cancer tissue | malignant pleural mesothelioma | [113] |
| | the expression of collagen III and collagen III mRNA | Ewing's sarcoma | [114] |
| Type IV | the type IV collagen, MMP-generated type IV collagen fragment in serum in serum | breast cancer | [101,105] |
| | 7S domain of type IV collagen in serum | gastric cancer; pancreatic cancer; lung cancer; extrahepatic cancer; hepatocellular carcinoma | [111,115–118] |
| | the expression level of collagen IV | malignancy glioma | [119] |
| | the differential localization of the type IV collagen alpha5/alpha6 chains | colorectal epithelial tumors | [120] |
| | MMP-degradation of type IV collagen | ovarian cancer | [121] |
| | the expression level of collagen IV | prostate cancer | [122] |
| | the expression of collagen type IV | urothelial carcinoma; oral squamous cell carcinoma | [123,124] |
| | the expression of the type IV collagen alpha1 and alpha2 chains | hepatocarcinogenesis | [125] |
| | the expression of the type IV collagen alpha1 | bladder cancer | [126] |
| | the expression of collagen IV in tumor location | invasive adenocarcinoma | [127] |
| | serum N-terminal pro-peptide of type IV collagen 7S domain | hepatocellular carcinoma in patients with liver cirrhosis | [128] |

**Table 1.** *Cont.*

| Collagen Type | Biomarker | Cancer Type | Reference |
|---|---|---|---|
| Type V | the expression level of collagen type V alpha 2 | colorectal cancer; gastric cancer; | [129,130] |
| | the expression level of collagen type V | breast cancer; lung cancer | [131,132] |
| Type VI | MMP-generated type III collagen fragment | breast cancer; colon cancer; gastric cancer; malignant melanoma; lung cancer; ovarian cancer; pancreas cancer; prostate cancer | [133] |
| | serum collagen type VI alpha 3 | pancreatic ductal adenocarcinoma | [134] |
| | stromal collagen type VI | salivary gland cancer | [135] |
| | the expression of COL6 | pancreatic cancer | [136] |
| | collagen type VI alpha 1chain | esophageal squamous cell carcinoma | [137] |
| Type VII | the expression level of type VII collagen | identifying lung cancer subtypes; skin cancer; gastric cancer | [138–140] |
| | the expression level of collagen type VII a 1 chain | clear cell renal cell carcinoma | [141] |
| Type VIII | the NC1 domain of human type VIII collagen a1 chain in serum | colorectal cancer | [142] |
| | collagen type VIII alpha 1 chain | breast cancer; colon Adenocarcinoma | [143,144] |
| Type XI | the expression level of Collagen Type XI Alpha 1 Chain | colorectal cancer; breast carcinoma invasiveness; colon cancer; gastric cancer; pancreatic ductal adenocarcinoma; pancreatic adenocarcinoma; pancreatic cancer | [145–151] |
| | the expression of procollagen XI Alpha 1 Chain | breast cancer | [152] |
| type XIII | the expression of the type XIII collagen alpha1 | bladder cancer | [126] |
| Type XIV | the expression of type XIV collagen | breast cancer | [153] |
| Type XV | fragments of collagen XV collagen alpha1 in urine | gastrointestinal cancer | [154] |
| Type XVIII | the expression of type XVIII collagen | pancreatic ductal adenocarcinoma | [155] |
| | serum endostatin (a fragment of collagen XVIII) levels | colorectal cancer | [156] |
| Type XXIII | the expression of collagen type XXIII alpha 1 chain | clear cell renal cell carcinoma | [157] |

*5.2. The Predictive Value of Collagens*

Collagens have high value in monitoring cancer processes, prognosis, and recurrence. The predictive value is exhibited in many types of cancer, including breast cancer, prostate adenocarcinoma, lung cancer, hepatocellular carcinoma, colon cancer, and pancreatic cancer. In breast cancer, the qualitative descriptors of collagens at the boundaries between tumor and stroma are important indicators for tumor staging. In invasive breast cancer, the 5-year disease-free survival in patients with low tumor-stromal ratios is poorer than the patients with high tumor–stroma ratios. In lung cancer, high levels of collagen I in serum and tissue demonstrated a significant decrease in survival. Furthermore, collagen metabolic components and prolyl hydroxylases have been marked as the predictive factors of lung cancer presence, progression, and outcome. Abnormal collagen expression is associated with cancer overall survival (OS). The prognosis value is outstanding in enriched stromal

cancers, such as pancreatic cancer and colon cancer. It is confirmed that the alignment of collagens was associated with the patient survival of pancreatic ductal adenocarcinoma (PDAC). Highly aligned collagen fibers report poor prognosis in PDAC, according to clinical statistics. Collagen types I, III, VI, and XI were shown to be associated with the diverse response of pancreatic cancers, such as proliferation, migration, decreasing E-cadherin expression, and cancer-associated fibroblasts [158]. Furthermore, the percent survival with a high level of collagen type I is observably lower than the low level. It was shown that the level of collagen type I had a negative correlation to OS for pancreatic cancer [159]. In colon cancer, the level of collagen expression is the key indicator to predicting the OS and risk, especially the types of COL1A1, COL1A2, COL3A1, COL4A3, and COL4A6. Please refer to reference [158] for more information on the predictive value of collagens.

## 6. Therapeutic Opportunities of Cancer Target to Collagens and the Collagen Associated Molecules

Collagen remodeling plays a significant role in cancer progression, as the content described above. It provides the possibility for therapeutic cancer targeting to collagens undergoing remodeling, including inhibiting the synthesis of collagens and interdicting the reactivator on the signal pathway. Of note, many small molecule inhibitors of collagen synthesis and functioning are available as anti-cancer drugs. They could accurately point to the target, avoiding damage to normal cells, which is an absolute advantage over conventional chemotherapeutic agents.

### 6.1. Inhibiting the Synthesis and Secretion of Collagens

Inhibiting collagen synthesis and secretion is a strategy for cancer therapeutics, which could prevent the series of effects initiated by collagen remodeling. For instance, as a catalyst in a key step of collagen biosynthesis, CP4H was linked with cancer metastasis in recent studies. Undoubtedly, CP4H has confirmed a new target for anti-cancer drugs. Several drugs targeted to CP4H have been developed as CP4H inhibitors, such as Ethyl 3,4-dihydroxybenzoate (EDHB) and 2-(5-carboxythiazol-2-yl) pyridine-5-carboxylic acid (pythiDC) [160]. Lysyl hydroxylation is a key step for collagen cross-link and deposition, which is a potential target to inhibit collagen synthesis. Aiming at the collagen remodeling induced by aberrant lysyl hydroxylation and collagen cross-link, lysyl hydroxylation is developed as a potential target for cancer therapeutic. Minoxidil, as an inhibitor of lysyl hydroxylation, is confirmed to have anti-invasive effects on human breast cancer [161]. Relatively, procollagen-lysine 2-oxoglutarate 5-dioxygenase (PLOD) drew much attention as the catalyzer of the process of lysyl hydroxylation. Increased PLOD expression has been detected in many types of cancer. Targeting PLODs is considered a potential strategy for cancer treatment; however, there are still no reports revealing the related anti-cancer drugs [162]. More available targets and the related drug aiming at collagen synthesis are summarized in Table 2.

**Table 2.** A summary of drugs targeting the synthesis and secretion of collagens.

| Therapeutics Target | Drug | Mechanism | Cancer Type | Status | Reference |
|---|---|---|---|---|---|
| collagen type I | Baicalein | inhibiting collagen type I transcription by alleviating TGF-β1 stimulation | lung cancer, osteosarcoma cells, bladder cancer, breast cancer, pancreatic cancer, cervical cancer, oral cancer | a promising candidate awaiting further testing | [163–165] |
| | Phenylbutyrate, sodium phenylbutyrate | as a weak histone deacetylase inhibitor decreasing collagen type I Alpha 1 mRNA transcription | lung cancer, prostate cancer, liver cancer, breast cancer, ovarian cancer, bladder cancer | a promising candidate awaiting further testing | [166–171] |

**Table 2.** *Cont.*

| Therapeutics Target | Drug | Mechanism | Cancer Type | Status | Reference |
|---|---|---|---|---|---|
| collagen type I | C9 | C9 inhibits collagen production by dissociating laribonucleoprotein domain family member 6 (LARP6) from type I collagen 50′SL RNA | - | awaiting further testing | [172] |
| | Ethyl 3,4-dihydroxybenzoate (EDHB), 2-(5-carboxythiazol-2-yl) pyridine-5-carboxylic acid (pythiDC) | inhibiting collagen synthesis by inhibiting Prolyl 4-hydroxylases (P4Hs), which is a synthesis and regulatory factor of collagen type I | colorectal cancer, breast cancer | awaiting further testing | [160,173,174] |
| | Minoxidil | inhibiting collagen synthesis by inhibitor lysyl hydroxylases (LHs), which is a synthesis and regulatory factor of collagen type I | prostate cancer, breast cancer, ovarian cancer | a promising candidate awaiting further testing | [161,162,175,176] |
| | AK-778 | inhibiting collagen synthesis by mitigating the interaction between collagen and HSP47, which is a molecule required for collagen type I maturation. | - | a promising candidate awaiting further testing | [177,178] |
| | CCT365623 | decreasing collagen synthesis by inhibiting lysyl oxidase (LOX), which is a regulatory factor for collagen cross-linking | - | a promising candidate awaiting further testing | [179,180] |
| collagen type XI | LY2157299 | inhibiting collagen XI alpha 1 chain (COL11A1) expression by inhibiting the transforming growth factor beta receptor 1 (TβRI) | ovarian cancer, pancreatic cancer, breast cancer | phase II clinical trial | [181–185] |
| | SC66 | as an Akt inhibitor preventing the transcription of COL11A1 | colon cancer, ovarian cancer, bladder cancer, lung cancer | under clinical trials | [182,186–189] |
| collagen type XI | AK778 and its cleavage product Col003 | disrupted collagen binding with the molecular chaperone HSP47 and inhibited collagen secretion | - | awaiting further clinical studies | [177,182] |

## 6.2. Interdicting the Receptors

The collagen receptors are the direct trigger of the interaction between cancer cells and collagens. Cancer cells sense the surrounding microenvironment by responding to the biochemical and mechanical properties of transmembrane receptors, including integrins and discoidin domain receptors (DDRs). Interdicting the receptors of collagens is another effectual strategy. We summarize the related targets and the corresponding drug below.

### 6.2.1. Integrins

Integrins are the important receptor of collagens on the cell membrane. It is a large family, at least including 24 different functional heterodimeric receptors distinguished by 18α-subunits and 8β-subunits [190,191]. According to the reports by far, the integrins of α1β1, α2β1, α3β1, α4β1, α5β1, α6β1, α9β1, α10β1, α11β1, α5β3, and α5β8 have been

found to be involved in tumor growth and metastasis by the regulation of collagen-binding integrin signal [190,192–200]. Further, integrin-mediated pathways are reported many times to connect to drug resistance [201,202]. So, integrins are considered an attractive drug target for cancer therapeutics [203]. This concept is largely encouraged by preclinical studies. Cilengitide, an inhibitor of integrin $\alpha v \beta 3$ and $\alpha v \beta v$, has been developed as an anti-cancer drug in various tumor types. Several clinical trials were carried out on diverse cancers, such as lung cancer, breast cancer, glioblastoma, prostate cancer, melanoma, and squamous cell cancer [204,205]. Abituzumab (EMD 525797), a monoclonal antibody targeting integrin alpha nu heterodimers, was also demonstrated as an anti-cancer drug. The phase I clinical trial was completed in ovarian cancer patients with liver metastases and the phase II clinical trial was completed in metastatic colorectal cancer; however, successful clinical trials are few in number. For example, cilengitide failed to improve survival for glioblastoma patients in the phase III trial, despite the standard care. At the same time, the trial data of combining abituzumab showed no improvement in the progression-free survival of patients compared with the standard of care alone. So, further verified trials are essential based on stratifying the patient population [206]. Exploiting tumor-specific integrin expression profiles or downstream integrin effectors is also an alternative strategy to target for the development of anti-cancer drugs. Many typical integrin activation factors are noticed, such as FAK, LOX, mucins, and the corresponding inhibitors are developed for cancer therapeutic. Moreover, snake venom disintegrins were confirmed to inhibit integrins and further effected cancer treatment. We summarize the data in Table 3 below.

**Table 3.** Integrin-associated therapy and the related drugs in cancer therapeutics.

| Therapeutics Target | Drug | Mechanism | Cancer Type | Status | Reference |
|---|---|---|---|---|---|
| integrin | Cilengitide | an inhibitor of integrin $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha 5 \beta 1$, $\alpha II \beta 3$ | lung cancer, breast cancer, glioblastoma, prostate cancer, melanoma, squamous cell cancer | in clinical trials | [203,207,208] |
| | Abituzumab | inhibiting integrin $\alpha v \beta 1$, $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha v \beta 6$, $\alpha v \beta 8$ | colorectal cancer. ovarian cancer | in clinical trials | [203,209] |
| | Etaracizumab | inhibiting integrin $\alpha v \beta 3$ | melanoma prostate cancer | a phase II trial | [203] |
| | Intetumumab | inhibiting integrin $\alpha v \beta 1$, $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha v \beta 6$, $\alpha v \beta 8$ | melanoma prostate cancer | a phase II trial | [203] |
| | NCT02428270 | using a FAK inhibitor in combination with a MEK1 and MEK2 inhibitor | pancreatic cancer | a phase II trial | [206] |
| | NCT02546531 | using a FAK inhibitor in combination with a humanized antibody targeting programmed cell death protein 1 (PD1) and chemotherapy | solid tumors pancreatic cancer | a phase I trial | [206] |
| | NCT01279603 | inhibit MUC1 cytoplasmic tail oligomerization | solid tumors | a phase I trial | [206] |
| | NCT00565721 | as valuable probes in cancer imaging studies to determine both prognosis and treatment efficacy | lung cancer Head & Neck cancer | a phase II trial | [206] |
| | NCT02683824 | an $\alpha v \beta 6$ integrin tracer to detect tumors and evaluate treatment response in patients with pancreatic cancer | pancreatic cancer | early phase I trial | [206] |

**Table 3.** *Cont.*

| Therapeutics Target | Drug | Mechanism | Cancer Type | Status | Reference |
|---|---|---|---|---|---|
| integrin | snake venom disintegrins | inhibiting integrins on transmembrane cellular surfaces | prostate breast cancer lung cancer sarcoma | a promising candidate awaiting further testing | [208] |

6.2.2. DDRs

Another important receptor is DDRs family, including DDR1 and DDR2, which have been proved to regulate various cellular signaling pathways, including cell proliferation, adhesion, migration, and matrix remodeling. DDRs are a subfamily of receptor tyrosine kinases, activated by the triple-helical structure of collagens in the interaction. It is revealed that DDRs possess a special activation mechanism, which initiates the pathways leading to autophosphorylation through collagen binding. In the fibrillar collagens, DDR1 and DDR2 could respond to collagen type I, II, III, and V, while in the non-fibrillar collagens, type IV, VI, VIII, and X are also the activator. However, the mechanism of extracellular collagen binding and activation of the cytosolic kinase domain of the receptors is not clear so far. A recognized theory is that DDRs occur dimerization before the ligand binding with collagens, which is different from the other receptor tyrosine kinases undergoing dimerization after ligand binding [210]; then, the amino acid produces residues of collagens as the sites bind with DDRs dimerization [211]. In turn, the activated DDRs could trigger the signal transduction pathways of cell behaviors, such as proliferation, migration, and invasion [212]. In many cancers, overexpression of DDRs is associated with a poor prognosis. Deng et al. demonstrated that collagen-induced DDR1 activation in cancer cells could recruit tumor-associated neutrophils to form extracellular traps, enhancing the subsequent cancer cell invasion and metastasis [213]. The imbalance expression of DDRs has been demonstrated to be associated with most cancers. Huo et al. revealed that high expression of DDR1 was associated with poor prognosis in pancreatic ductal adenocarcinoma [214]. Xie et al. found that overexpression of DDR1 promoted the aggressive growth, migration, and invasion of bladder cancer cells, in which process collagen IV was a signal axis [215]. As DDRs play a significant role in cancer progression, DDRs would be new promising targets for cancer treatment, such as the design of DDR inhibitors for use in clinical settings. Some drugs were developed to inhibit DDR expression, such as dasatinib, imatinib, nilotinib, and ponatinib. Dasatinib was confirmed enabling to inhibit gastric cancer cell migration and invasion in the assays. Several clinical trials were completed in phases I and II, such as lung cancer, breast cancer, and prostate cancer. Nilotinib was reported to reduce metastatic colorectal cancer invasion by inhibiting DDR1 kinase activation. Many clinical trials are currently underway in several types of cancer, such as breast cancer, gastrointestinal stromal tumors, and so on. The antibody–drug conjugate targeting DDRs is utilized in anti-cancer drug development. As an example, T4H11-DM4 is demonstrated to be effective for colon cancer. Many other drugs were developed to target DDRs in recent years—shown in Table 4.

**Table 4.** DDRs associated therapy and the related drugs in cancer therapeutics.

| Therapeutics Target | Drug | Mechanism | Cancer Type | Status | Reference |
|---|---|---|---|---|---|
| DDRs | nilotinib | inhibiting the kinase activity of DDR1 | colorectal cancer | | [216] |
| | Dasatinib | inhibit DDRs | prostate cancer, glioblastoma, breast cancer, lung cancer, gastric cancer | in clinical trials | [217–223] |
| | Nilotinib | inhibit DDRs | colorectal cancer, colon cancer | in clinical trials | [217,224–226] |

**Table 4.** *Cont.*

| Therapeutics Target | Drug | Mechanism | Cancer Type | Status | Reference |
|---|---|---|---|---|---|
| DDRs | Imatinib | inhibit DDRs | lung cancer, liver cancer | in clinical trials | [227–230] |
| | Ponatinib | inhibit DDRs | lung cancer | in clinical trials | [231,232] |
| | T4H11-DM4 | an antibody-drug conjugate targeting DDR1 | colon cancer | awaiting further clinical studies | [233] |
| | Actinomycin D | an antagonist of the DDR2-collagen interaction | rhabdomyosarcoma, Ewing's sarcoma, trophoblastic neoplasia, and testicular carcinoma | in clinical application | [234,235] |
| | LCB 03-0110 | inhibiting collagen-induced activation of DDR1 and DDR2 receptors | - | awaiting further clinical studies | [236,237] |
| | pyrazolo-urea containing compounds 2a, 4a, 4b | inhibit DDR2 | - | awaiting further clinical studies | [238] |
| | 7rh | inhibited the kinase activity of DDR1 | gastric cancer, nasopharyngeal carcinoma, pancreatic ductal adenocarcinoma, breast cancer, uveal melanoma | in clinical trials | [218,239–243] |
| | 7rj | inhibited the kinase activity of DDR1 | - | awaiting further clinical studies | [235] |
| | DDR1-IN-1 | induced a significant inhibitory effect against DDR1 | colorectal cancer, lung cancer | awaiting further clinical studies | [232,244–246] |
| | DDR1-IN-2 | induced a significant inhibitory effect against DDR1 | - | awaiting further clinical studies | [235] |
| | miR-199a-5p, a targeted delivery of miRNAs | inhibit DDRs | colorectal cancer, renal cancer | awaiting further clinical studies | [247–250] |
| | monoclonal antibodies Fab 3E3, 48B3, H-126 | inhibit DDRs | ductal breast carcinoma | awaiting further clinical studies | [235,251] |

### 6.3. Targeting to Collagen-Induced Chemoresistance

More and more data implicated the desmoplastic reaction is substantially related to chemoresistance in chemotherapeutics. It is reported that the pancreatic cancer cells grown in collagens demonstrated low sensitivity to gemcitabine chemotherapy. A further study showed that three-dimensional collagens enabled an increase in ERK1/2 signaling, which is known to promote chemotherapy resistance in several cancers. In other malignancies, it is repeatedly reported that collagens protect cancer cells against chemotherapy. For instance, in lung cancer models, collagens are shown to provide survival signals to attenuate the effects of chemotherapy. In this regard, MT1-MMP plays a critical physiological role in modulating growth factors and integrin signaling to enhance ERK1/2 phosphorylation in the collagen microenvironment. Moreover, the increasing density of the ECM initiated by collagen fibers and collagen deposition attenuates the permeability of drug delivery in chemotherapy. Targeting collagen-induced chemoresistance is an effective strategy to promote the chemotherapy effect. Some drugs are developed targeting the intermediary in the signal pathway. Moreover, enhancing the collagen penetration of anticancer drugs is an available strategy for cancer therapeutics, which targets collagen-associated stiffness ECM and high dense collagen fibers, increasing the drug efficacy [252]. We summarize the related drugs in Table 5.

**Table 5.** The drugs that target collagen-induced chemoresistance.

| Therapeutics Target | Drug | Mechanism | Cancer Type | Status | Reference |
|---|---|---|---|---|---|
| collagen | polyethylene glycol (PEG) & glutaraldehyde co-modified fluorinated chitosan (PGFCS) | as a collagen-targeted transepithelial penetration enhancer creating a tumor-targeted adhesive interface to open the transepithelial-delivery barrier at the tumor site | bladder cancer | awaiting further testing | [253] |
| | losartan | reducing stromal collagen and hyaluronan production to decompress tumor vessels for enhancing drug delivery. | prostate cancer, colorectal cancer, pancreatic cancer, breast cancer, lung cancer, ovarian cancer, endometrial cancer | in clinical application | [254–261] |
| Collagen type II | Ivosideni | a selective inhibitor of mutant IDH1, which is a gene mutant site of collagen type II | chondrosarcoma | waiting further clinical studies | [262] |
| ERK1/2 | JaZ-30 | downregulates phosphorylation of the extracellular signal-regulated ERK1/2 | melanoma | waiting further clinical studies | [263] |

## 7. Conclusions and Future Perspectives

Collagens are the main component of the ECM, and their remodeling occurs along with all processes of cancer progression. Collagens occur in abnormal morphology and distribution in precancerous lesions, which seriously affect the topography of the ECM. This provides a chance for clinicians to discover the pathology through medical imaging or pathological for cancer early diagnosis. In cancer development, collagens cause different stages of ECM topography, which contributes to cancer staging. Moreover, collagen-associated biochemical indicators are the significant biomarkers of cancer diagnosis and prognosis. Collagen participation in cancer progression is not only reflected in the remodeling under the influence of tumor cells or tumor-associated cells but is further revealed as the role of guider or inducer for cancer cell invasion. The "highway" for cancer cell invasion and the high stiffness of ECM are all enhanced by collagens, corresponding with the aligned collagen fiber bundle and collagen deposition, respectively. Based on the mechanism of the interaction between collagens and cancer cells, many opportunities for cancer therapeutics are revealed by disturbing or blocking the requirement in the interaction. The targets are diversely located across the pathway of collagen synthesis, binding to receptors, degradation, and drug transport. Overall, collagens provide many opportunities, whether for cancer diagnosis or cancer treatment; however, there are still many challenges from the exploration of therapeutic targets to drug development because there are only a few drugs allowed to enter the clinical application, while most of them are just in clinical trials or waiting for further clinical studies. Several questions and propositions are provided for further research. Firstly, the mechanism of collagen remodeling and its interaction with cancer cells is not completely clear. So further studies are essential on the mechanisms of collagen remodeling and the interaction between collagens and cancer cells. In our opinion, small molecule inhibitors are worth developing as anti-cancer drugs due to their excellent location and potential to cause no damage to normal cells. It would be a potential strategy to block the collagen remodeling; however, it is hard to implement for the reconstructed collagens. So, how to reduce the effectiveness of the reconstructed collagens is a valuable issue. In addition to the targets in the action pathway, we propose that ablating the reconstructed collagens is another strategy for cancer therapeutics. Moreover, to enhance the efficacy, we highlight the significance of finding a suitable nanocarrier to increase the drug transport capacity. Overall, further efforts are urgent in the collagen-associated mechanism and the therapeutic strategy for cancer.

## References

1. Paszek, M.J.; Zahir, N.; Johnson, K.R.; Lakins, J.N.; Rozenberg, G.I.; Gefen, A.; Reinhart-King, C.A.; Margulies, S.S.; Dembo, M.; Boettiger, D.; et al. Tensional homeostasis and the malignant phenotype. *Cancer Cell* **2005**, *8*, 241–254. [CrossRef] [PubMed]
2. Butcher, D.T.; Alliston, T.; Weaver, V.M. A tense situation: Forcing tumour progression. *Nat. Rev. Cancer* **2009**, *9*, 108–122. [CrossRef] [PubMed]
3. Theocharis, A.D.; Skandalis, S.S.; Gialeli, C.; Karamanos, N.K. Extracellular matrix structure. *Adv. Drug Deliv. Rev.* **2016**, *97*, 4–27. [CrossRef] [PubMed]
4. Winkler, J.; Abisoye-Ogunniyan, A.; Metcalf, K.J.; Werb, Z. Concepts of extracellular matrix remodelling in tumour progression and metastasis. *Nat. Commun.* **2020**, *11*, 5120. [CrossRef]
5. Frantz, C.; Stewart, K.M.; Weaver, V.M. The extracellular matrix at a glance. *J. Cell Sci.* **2010**, *123*, 4195–4200. [CrossRef] [PubMed]
6. Ricard-Blum, S. The Collagen Family. *Cold Spring Harbor Perspect. Biol.* **2011**, *3*, a004978. [CrossRef]
7. Wu, Y.X.; Ge, G.X. Complexity of type IV collagens: From network assembly to function. *Biol. Chem.* **2019**, *400*, 565–574. [CrossRef]
8. Bella, J.; Hulmes, D.J.S. Fibrillar Collagens. In *Fibrous Proteins: Structures and Mechanisms*; Parry, D.A.D., Squire, J.M., Eds.; Springer: Berlin/Heidelberg, Germany, 2017; Volume 82, pp. 457–490.
9. Shamhart, P.E.; Meszaros, J.G. Non-fibrillar collagens: Key mediators of post-infarction cardiac remodeling? *J. Mol. Cell. Cardiol.* **2010**, *48*, 530–537. [CrossRef]
10. Ambekar, R.; Lau, T.-Y.; Walsh, M.; Bhargava, R.; Toussaint, K.C., Jr. Quantifying collagen structure in breast biopsies using second-harmonic generation imaging. *Biomed. Opt. Express* **2012**, *3*, 2021–2035. [CrossRef]
11. Belisle, J.; Zigras, T.; Costantino, S.; Cartier, R.; Butany, J.; Wiseman, P.W.; Leask, R.L. Second harmonic generation microscopy to investigate collagen configuration: A pericarditis case study. *Cardiovasc. Pathol. Off. J. Soc. Cardiovasc. Pathol.* **2010**, *19*, e125–e128. [CrossRef]
12. Grethel Fuentes-Corona, C.; Licea-Rodriguez, J.; Younger, R.; Rangel-Rojo, R.; Potma, E.O.; Rocha-Mendoza, I. Second harmonic generation signal from type I collagen fibers grown in vitro. *Biomed. Opt. Express* **2019**, *10*, 6449–6461. [CrossRef] [PubMed]
13. Mohammed, D.; Pardon, G.; Versaevel, M.; Bruyere, C.; Alaimo, L.; Luciano, M.; Vercruysse, E.; Pruitt, B.L.; Gabriele, S. Producing Collagen Micro-stripes with Aligned Fibers for Cell Migration Assays. *Cell. Mol. Bioeng.* **2020**, *13*, 87–98. [CrossRef] [PubMed]
14. Okoro, C.; Toussaint, K.C., Jr. Second-harmonic patterned polarization-analyzed reflection confocal microscope. *J. Biomed. Opt.* **2017**, *22*, 086007. [CrossRef] [PubMed]
15. Olivares, V.; Condor, M.; Del Amo, C.; Asin, J.; Borau, C.; Manuel Garcia-Aznar, J. Image-based Characterization of 3D Collagen Networks and the Effect of Embedded Cells. *Microsc. Microanal.* **2019**, *25*, 971–981. [CrossRef]
16. Xu, M.Y.; Liu, J.; Sun, J.Y.; Xu, X.R.; Hu, Y.C.; Liu, B. Optical Microscopy and Electron Microscopy for the Morphological Evaluation of Tendons: A Mini Review. *Orthop. Surg.* **2020**, *12*, 366–371. [CrossRef]
17. Raspanti, M.; Reguzzoni, M.; Rita Basso, P.; Protasoni, M.; Martini, D. Visualizing the Supramolecular Assembly of Collagen. *Methods Mol. Biol.* **2019**, *1952*, 33–44. [PubMed]
18. Oosterlaken, B.M.; Friedrich, H.; de With, G. The effects of washing a collagen sample prior to TEM examination. *Microsc. Res. Tech.* **2022**, *85*, 412–417. [CrossRef]
19. Quan, B.D.; Sone, E.D. Cryo-TEM Analysis of Collagen Fibrillar Structure. In *Research Methods in Biomineralization Science*; Yoreo, J.J.D., Ed.; Elsevier: Amsterdam, The Netherlands, 2013; Volume 532, pp. 189–205.
20. Oosterlaken, B.M.; van Rijt, M.M.J.; Joosten, R.R.M.; Bomans, P.H.H.; Friedrich, H.; de With, G. Time-Resolved Cryo-TEM Study on the Formation of Iron Hydroxides in a Collagen Matrix. *ACS Biomater. Sci. Eng.* **2021**, *7*, 3123–3131. [CrossRef]
21. Quan, B.D.; Sone, E.D. Structural changes in collagen fibrils across a mineralized interface revealed by cryo-TEM. *Bone* **2015**, *77*, 42–49. [CrossRef]
22. Raspanti, M.; Protasoni, M.; Manelli, A.; Guizzardi, S.; Mantovani, V.; Sala, A. The extracellular matrix of the human aortic wall: Ultrastructural observations by FEG-SEM and by tapping-mode AFM. *Micron* **2006**, *37*, 81–86. [CrossRef]
23. Stylianou, A. Assessing Collagen D-Band Periodicity with Atomic Force Microscopy. *Materials* **2022**, *15*, 1608. [CrossRef] [PubMed]
24. Youn, Y.-S.; Kim, S. Real-time atomic force microscopy imaging of collagen fibril under ultraviolet irradiation. *J. Ind. Eng. Chem.* **2016**, *42*, 15–18. [CrossRef]
25. Meek, K.M.; Quantock, A.J. The use of X-ray scattering techniques to determine corneal ultrastructure. *Prog. Retin. Eye Res.* **2001**, *20*, 95–137. [CrossRef]

26. Meek, K.M.; Quantock, A.J.; Hayes, S.; Bell, J. X-Ray Diffraction Imaging of Corneal Ultrastructure. *Methods Mol. Biol.* **2020**, *2145*, 231–247. [PubMed]

27. Karjalainen, V.P.; Kestila, I.; Finnila, M.A.; Folkesson, E.; Turkiewicz, A.; Onnerfjord, P.; Hughes, V.; Tjonstand, J.; Englund, M.; Saarakkala, S. Quantitative three-dimensional collagen orientation analysis of human meniscus posterior horn in health and osteoarthritis using micro-computed tomography. *Osteoarthr. Cartil.* **2021**, *29*, 762–772. [CrossRef]

28. Eder, J.; Tonar, Z.; Schmid-Schwap, M.; Bristela, M.; Skolka, A.; Traxler, H.; Piehslinger, E.; Egerbacher, M.; Trattnig, S.; Witter, K. Regional Collagen Fiber Network in the Articular Disc of the Human Temporomandibular Joint: Biochemical 3-Tesla Quantitative Magnetic Resonance Imaging Compared to Quantitative Histologic Analysis of Fiber Arrangement. *J. Oral Facial Pain Headache* **2018**, *32*, 266–276. [CrossRef]

29. Mercado, K.P.; Helguera, M.; Hocking, D.C.; Dalecki, D. Noninvasive Quantitative Imaging of Collagen Microstructure in Three-Dimensional Hydrogels Using High-Frequency Ultrasound. *Tissue Eng. Part C-Methods* **2015**, *21*, 671–682. [CrossRef]

30. Hagan, K.L.; Hullfish, T.; Casey, E.; Raxter, J.R. Tendon structure quantified using ultrasound imaging differs based on location and training type. *J. Appl. Physiol.* **2018**, *125*, 1743–1748. [CrossRef]

31. Kim, M.N.; Kim, S.U.; Kim, B.K.; Park, J.Y.; Kim, D.Y.; Ahn, S.H.; Song, K.J.; Park, Y.N.; Han, K.H. Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with transient elastography-defined subclinical cirrhosis. *Hepatology* **2015**, *61*, 1851–1859. [CrossRef]

32. Suh, B.; Park, S.; Shin, D.W.; Yun, J.M.; Yang, H.K.; Yu, S.J.; Shin, C.I.; Kim, J.S.; Ahn, E.; Lee, H.; et al. High Liver Fibrosis Index FIB-4 Is Highly Predictive of Hepatocellular Carcinoma in Chronic Hepatitis B Carriers. *Hepatology* **2015**, *61*, 1261–1268. [CrossRef]

33. Baglieri, J.; Brenner, D.A.; Kisseleva, T. The Role of Fibrosis and Liver-Associated Fibroblasts in the Pathogenesis of Hepatocellular Carcinoma. *Int. J. Mol. Sci.* **2019**, *20*, 1723. [CrossRef]

34. Jeganathan, N.; Cleland, D.; Sathananthan, M. The association of lung cancer with pulmonary fibrosis. *ERJ Open Res.* **2022**, *8*, 00505-2021. [CrossRef] [PubMed]

35. Saha, R.; Ryan, D.; Hanrahan, E.; Dodd, J.D. Early detection of recurrent lung cancer: Enhancing-nodule in post-radiation fibrosis. *Acta Radiol. Open* **2022**, *11*, 20584601211072280. [CrossRef]

36. Snijder, J.; Peraza, J.; Padilla, M.; Capaccione, K.; Salvatore, M.M. Pulmonary fibrosis: A disease of alveolar collapse and collagen deposition. *Expert Rev. Respir. Med.* **2019**, *13*, 615–619. [CrossRef]

37. Liu, C.M.; Liao, Y.W.; Hsieh, P.L.; Yu, C.H.; Chueh, P.J.; Lin, T.C.; Yang, P.Y.; Yu, C.C.; Chou, M.Y. miR-1246 as a therapeutic target in oral submucosa fibrosis pathogenesis. *J. Formos. Med. Assoc.* **2019**, *118*, 1093–1098. [CrossRef] [PubMed]

38. Shih, Y.-H.; Wang, T.-H.; Shieh, T.-M.; Tseng, Y.-H. Oral Submucous Fibrosis: A Review on Etiopathogenesis, Diagnosis, and Therapy. *Int. J. Mol. Sci.* **2019**, *20*, 2940. [CrossRef] [PubMed]

39. Despotovic, S.Z.; Milkcvic, D.N.; Krmpot, A.J.; Pavlovic, A.M.; Zivanovic, V.D.; Krivokapic, Z.; Pavlovic, V.B.; Levic, S.; Nikolic, G.; Rabasovic, M.D. Altered organization of collagen fibers in the uninvolved human colon mucosa 10 cm and 20 cm away from the malignant tumor. *Sci. Rep.* **2020**, *10*, 6359. [CrossRef]

40. de Fatima Cavalcanti Castor, M.d.G.; Torres, L.C.; Vieira de Mello, R.J.; Natal, R.d.A.; Vassallo, J. Study on collagen parameters in vulvar cancer and preneoplastic lesions by Second Harmonic Generation microscopy. *Sci. Rep.* **2020**, *10*, 5568. [CrossRef]

41. Zaffar, M.; Pradhan, A. Mapping of retardance, diattenuation and polarizance vector on Poincare sphere for diagnosis and classification of cervical precancer. *J. Biophotonics* **2020**, *13*, e201960139. [CrossRef]

42. Zaffar, M.; Pradhan, A. Assessment of anisotropy of collagen structures through spatial frequencies of Mueller matrix images for cervical pre-cancer detection. *Appl. Opt.* **2020**, *59*, 1237–1248. [CrossRef]

43. Hirakawa, Y.; Futaki, S.; Tanizaki, H.; Furukawa, F.; Maemura, K.; Kondo, Y.; Moriwaki, S. Enhanced expression of nidogen 1 around the nest of basal cell carcinoma compared with that around squamous cell carcinoma. *Med. Mol. Morphol.* **2019**, *52*, 99–105. [CrossRef] [PubMed]

44. Wu, Y.; Fu, F.M.; Lian, Y.N.; Nie, Y.T.; Zhuo, S.M.; Wang, C.; Chen, J.X. Monitoring the progression from intraductal carcinoma to invasive ductal carcinoma based on multiphoton microscopy. *J. Biomed. Opt.* **2015**, *20*, 096007. [CrossRef] [PubMed]

45. Banerjee, S.; Lo, W.C.; Majumder, P.; Roy, D.; Ghorai, M.; Shaikh, N.K.; Kant, N.; Shekhawat, M.S.; Gadekar, V.S.; Ghosh, S.; et al. Multiple roles for basement membrane proteins in cancer progression and EMT. *Eur. J. Cell Biol.* **2022**, *101*, 151220. [CrossRef]

46. Chang, J.L.; Chaudhuri, O. Beyond proteases: Basement membrane mechanics and cancer invasion. *J. Cell Biol.* **2019**, *218*, 2456–2469. [CrossRef]

47. Gaiko-Shcherbak, A.; Eschenbruch, J.; Kronenberg, N.M.; Teske, M.; Wolters, B.; Springer, R.; Gather, M.C.; Merkel, R.; Hoffmann, B.; Noetzel, E. Cell Force-Driven Basement Membrane Disruption Fuels EGF- and Stiffness-Induced Invasive Cell Dissemination from Benign Breast Gland Acini. *Int. J. Mol. Sci.* **2021**, *22*, 3962. [CrossRef] [PubMed]

48. Luthold, C.; Hallal, T.; Labbe, D.P.; Bordeleau, F. The Extracellular Matrix Stiffening: A Trigger of Prostate Cancer Progression and Castration Resistance? *Cancers* **2022**, *14*, 2887. [CrossRef] [PubMed]

49. Fang, M.; Yuan, J.; Peng, C.; Li, Y. Collagen as a double-edged sword in tumor progression. *Tumor Biol.* **2014**, *35*, 2871–2882. [CrossRef]

50. Leventhal, K.R.; Yu, H.M.; Kass, L.; Lakins, J.N.; Egeblad, M.; Erler, J.T.; Fong, S.F.T.; Csiszar, K.; Giaccia, A.; Weninger, W.; et al. Matrix Crosslinking Forces Tumor Progression by Enhancing Integrin Signaling. *Cell* **2009**, *139*, 891–906. [CrossRef]

51. Barbazan, J.; Vignjevic, D.M. Cancer associated fibroblasts: Is the force the path to the dark side? *Curr. Opin. Cell Biol.* **2019**, *56*, 71–79. [CrossRef]

52. Bertero, T.; Oldham, W.M.; Grasset, E.M.; Bourget, I.; Boulter, E.; Pisano, S.; Hofman, P.; Bellvert, F.; Meneguzzi, G.; Bulavin, D.V.; et al. Tumor-Stroma Mechanics Coordinate Amino Acid Availability to Sustain Tumor Growth and Malignancy. *Cell Metab.* **2019**, *29*, 124–140.e10. [CrossRef]

53. Stylianou, A.; Gkretsi, V.; Louca, M.; Zacharia, L.C.; Stylianopoulos, T. Collagen content and extracellular matrix cause cytoskeletal remodelling in pancreatic fibroblasts. *J. R. Soc. Interface* **2019**, *16*, 20190226. [CrossRef] [PubMed]

54. Stylianou, A.; Gkretsi, V.; Stylianopoulos, T. Transforming growth factor-beta modulates pancreatic cancer associated fibroblasts cell shape, stiffness and invasion. *Biochim. Et Biophys. Acta-Gen. Subj.* **2018**, *1862*, 1537–1546. [CrossRef] [PubMed]

55. Shibata, M.; Ham, K.; Hoque, M.O. A time for YAP1: Tumorigenesis, immunosuppression and targeted therapy. *Int. J. Cancer* **2018**, *143*, 2133–2144. [CrossRef] [PubMed]

56. Farhat, A.; Ferns, G.A.; Ashrafi, K.; Arjmand, M.-H. Lysyl Oxidase Mechanisms to Mediate Gastrointestinal Cancer Progression. *Gastrointest. Tumors* **2021**, *8*, 33–40. [CrossRef]

57. Azimzade, Y.; Saberi, A.A.; Sahimi, M. Regulation of migration of chemotactic tumor cells by the spatial distribution of collagen fiber orientation. *Phys. Rev. E* **2019**, *99*, 062414. [CrossRef]

58. Geiger, F.; Schnitzler, L.G.; Brugger, M.S.; Westerhausen, C.; Engelke, H. Directed invasion of cancer cell spheroids inside 3D collagen matrices oriented by microfluidic flow in experiment and simulation. *PLoS ONE* **2022**, *17*, e0264571. [CrossRef]

59. Han, W.; Chen, S.; Yuan, W.; Fan, Q.; Tian, J.; Wang, X.; Chen, L.; Zhang, X.; Wei, W.; Liu, R.; et al. Oriented collagen fibers direct tumor cell intravasation. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 11208–11213. [CrossRef]

60. Suveges, S.; Chamseddine, I.; Rejniak, K.A.; Eftimie, R.; Trucu, D. Collective Cell Migration in a Fibrous Environment: A Hybrid Multiscale Modelling Approach. *Front. Appl. Math. Stat.* **2021**, *7*, 680029. [CrossRef]

61. Gkretsi, V.; Stylianopoulos, T. Cell Adhesion and Matrix Stiffness: Coordinating Cancer Cell invasion and Metastasis. *Front. Oncol.* **2018**, *8*, 145. [CrossRef]

62. Li, H.; Bera, K.; Gilmore, H.; Davidson, N.E.; Goldstein, L.J.; Madabhushi, A. Histomorphometric measure of disorder of collagen fiber orientation is associated with risk of recurrence in ER plus breast cancers in ECOG-ACRIN E2197 and TCGA-BRCA. *Cancer Res.* **2020**, *80*, 615.

63. Lee, B.; Konen, J.; Wilkinson, S.; Marcus, A.I.; Jiang, Y. Local alignment vectors reveal cancer cell-induced ECM fiber remodeling dynamics. *Sci. Rep.* **2017**, *7*, 39498. [CrossRef] [PubMed]

64. Lewis, D.M.; Tang, V.; Jain, N.; Isser, A.; Xia, Z.; Gerecht, S. Collagen Fiber Architecture Regulates Hypoxic Sarcoma Cell Migration. *ACS Biomater. Sci. Eng.* **2018**, *4*, 400–409. [CrossRef] [PubMed]

65. Nan, H.; Liang, L.; Chen, G.; Liu, L.; Liu, R.; Jiao, Y. Realizations of highly heterogeneous collagen networks via stochastic reconstruction for micromechanical analysis of tumor cell invasion. *Phys. Rev. E* **2018**, *97*, 033311. [CrossRef] [PubMed]

66. Wang, H.; Abhilash, A.S.; Chen, C.S.; Wells, R.G.; Shenoy, V.B. Long-Range Force Transmission in Fibrous Matrices Enabled by Tension-Driven Alignment of Fibers. *Biophys. J.* **2014**, *107*, 2592–2603. [CrossRef] [PubMed]

67. Wang, J.; Petefish, J.W.; Hillier, A.C.; Schneider, I.C. Epitaxially Grown Collagen Fibrils Reveal Diversity in Contact Guidance Behavior among Cancer Cells. *Langmuir* **2015**, *31*, 307–314. [CrossRef]

68. Ray, A.; Provenzano, P.P. Aligned forces: Origins and mechanisms of cancer dissemination guided by extracellular matrix architecture. *Curr. Opin. Cell Biol.* **2021**, *72*, 63–71. [CrossRef] [PubMed]

69. Bayer, S.V.H.; Grither, W.R.; Brenot, A.; Hwang, P.Y.; Barcus, C.E.; Ernst, M.; Pence, P.; Walter, C.; Pathak, A.; Longmore, G.D. DDR2 controls breast tumor stiffness and metastasis by regulating integrin mediated mechanotransduction in CAFs. *Elife* **2019**, *8*, e45508. [CrossRef]

70. Hanley, C.J.; Noble, F.; Ward, M.; Bullock, M.; Drifka, C.; Mellone, M.; Manousopoulou, A.; Johnston, H.E.; Johnston, H.E.; Hayden, A.; et al. A subset of myofibroblastic cancer-associated fibroblasts regulate collagen fiber elongation, which is prognostic in multiple cancers. *Oncotarget* **2016**, *7*, 6159–6174. [CrossRef] [PubMed]

71. Del Amo, C.; Olivares, V.; Condor, M.; Blanco, A.; Santolaria, J.; Asin, J.; Borau, C.; Garcia-Aznar, J.M. Matrix architecture plays a pivotal role in 3D osteoblast migration: The effect of interstitial fluid flow. *J. Mech. Behav. Biomed. Mater.* **2018**, *83*, 52–62. [CrossRef]

72. Balcioglu, H.E.; van de Water, B.; Danen, E.H.J. Tumor-induced remote ECM network orientation steers angiogenesis. *Sci. Rep.* **2016**, *6*, 22580. [CrossRef]

73. Kirkpatrick, N.D.; Andreou, S.; Hoying, J.B.; Utzinger, U. Live imaging of collagen remodeling during angiogenesis. *Am. J. Physiol.-Heart Circ. Physiol.* **2007**, *292*, H3198–H3206. [CrossRef] [PubMed]

74. Luthria, G.; Li, R.; Wang, S.; Prytyskach, M.; Kohler, R.H.; Lauffenburger, D.A.; Mitchison, T.J.; Weissleder, R.; Miller, M.A. In vivo microscopy reveals macrophage polarization locally promotes coherent microtubule dynamics in migrating cancer cells. *Nat. Commun.* **2020**, *11*, 3521. [CrossRef] [PubMed]

75. Hansen, N.U.B.; Willumsen, N.; Sand, J.M.B.; Larsen, L.; Karsdal, M.A.; Leeming, D.J. Type VIII collagen is elevated in diseases associated with angiogenesis and vascular remodeling. *Clin. Biochem.* **2016**, *49*, 903–908. [CrossRef]

76. Piotrowski-Daspit, A.S.; Nerger, B.A.; Wolf, A.E.; Sundaresan, S.; Nelson, C.M. Dynamics of Tissue-Induced Alignment of Fibrous Extracellular Matrix. *Biophys. J.* **2017**, *113*, 702–713. [CrossRef] [PubMed]

77. Velez, D.O.; Tsui, B.; Goshia, T.; Chute, C.L.; Han, A.; Carter, H.; Fraley, S.I. 3D collagen architecture induces a conserved migratory and transcriptional response linked to vasculogenic mimicry. *Nat. Commun.* **2017**, *8*, 1651. [CrossRef]

78. Bedal, K.B.; Grassel, S.; Spanier, G.; Reichert, T.E.; Bauer, R.J. The NC11 domain of human collagen XVI induces vasculogenic mimicry in oral squamous cell carcinoma cells. *Carcinogenesis* **2015**, *36*, 1429–1439. [CrossRef]

79. Fan, H.; Li, H.; Liu, G.; Cong, W.; Zhao, H.; Cao, W.; Zheng, J. Doxorubicin combined with low intensity ultrasound suppresses the growth of oral squamous cell carcinoma in culture and in xenografts. *J. Exp. Clin. Cancer Res.* **2017**, *36*, 163. [CrossRef]

80. Nelson, M.T.; Short, A.; Cole, S.L.; Gross, A.C.; Winter, J.; Eubank, T.D.; Lannutti, J.J. Preferential, enhanced breast cancer cell migration on biomimetic electrospun nanofiber 'cell highways'. *Bmc Cancer* **2014**, *14*, 825. [CrossRef]

81. Su, C.-Y.; Burchett, A.; Dunworth, M.; Choi, J.S.; Ewald, A.J.; Ahn, E.H.; Kim, D.-H. Engineering a 3D collective cancer invasion model with control over collagen fiber alignment. *Biomaterials* **2021**, *275*, 120922. [CrossRef]

82. Gritsenko, P.G.; Ilina, O.; Friedl, P. Interstitial guidance of cancer invasion. *J. Pathol.* **2012**, *226*, 185–199. [CrossRef]

83. Iuliano, J.N.; Kutscha, P.D.; Biderman, N.J.; Subbaram, S.; Groves, T.R.; Tenenbaum, S.A.; Hempel, N. Metastatic bladder cancer cells distinctively sense and respond to physical cues of collagen fibril-mimetic nanotopography. *Exp. Biol. Med.* **2015**, *240*, 601–610. [CrossRef] [PubMed]

84. Soon, L.L. A discourse on cancer cell chemotaxis: Where to from here? *Iubmb Life* **2007**, *59*, 60–67. [CrossRef]

85. Yokoi, K.; Kojic, M.; Milosevic, M.; Tanei, T.; Ferrari, M.; Ziemys, A. Capillary-Wall Collagen as a Biophysical Marker of Nanotherapeutic Permeability into the Tumor Microenvironment. *Cancer Res.* **2014**, *74*, 4239–4246. [CrossRef]

86. Yudasaka, M.; Okamatsu-Ogura, Y.; Tanaka, T.; Saeki, K.; Kataura, H. Cold-induced Conversion of Connective Tissue Skeleton in Brown Adipose Tissues. *Acta Histochem. Et Cytochem.* **2021**, *54*, 131–141. [CrossRef] [PubMed]

87. Knudson, K.M.; Hicks, K.C.; Luo, X.; Chen, J.Q.; Schlom, J.; Gameiro, S.R. M7824, a novel bifunctional anti-PD-L1/TGFβ Trap fusion protein, promotes anti-tumor efficacy as monotherapy and in combination with vaccine. *Oncoimmunology* **2018**, *7*, e1426519. [CrossRef] [PubMed]

88. Romer, A.M.A.; Thorseth, M.L.; Madsen, D.H. Immune Modulatory Properties of Collagen in Cancer. *Front. Immunol.* **2021**, *12*, 791453. [CrossRef]

89. Yu, Q.; Xue, Y.X.; Liu, J.; Xi, Z.; Li, Z.; Liu, Y.H. Fibronectin Promotes the Malignancy of Glioma Stem-Like Cells Via Modulation of Cell Adhesion, Differentiation, Proliferation and Chemoresistance. *Front. Mol. Neurosci.* **2018**, *11*, 130. [CrossRef]

90. Fang, M.; Yuan, J.-P.; Peng, C.-W.; Liu, S.-P.; Li, Y. Dynamic Changes of Collagen IV During Cancer Invasion and Migration: Pulse Mode. *Prog. Biochem. Biophys.* **2013**, *40*, 1056–1062.

91. Zhang, H.; Fredericks, T.; Xiong, G.; Qi, Y.; Rychahou, P.G.; Li, J.-D.; Pihlajaniemi, T.; Xu, W.; Xu, R. Membrane associated collagen XIII promotes cancer metastasis and enhances anoikis resistance. *Breast Cancer Res.* **2018**, *20*, 116. [CrossRef]

92. Karagiannis, G.S.; Petraki, C.; Prassas, I.; Saraon, P.; Musrap, N.; Dimitromanolakis, A.; Diamandis, E.P. Proteomic Signatures of the Desmoplastic Invasion Front Reveal Collagen Type XII as a Marker of Myofibroblastic Differentiation During Colorectal Cancer Metastasis. *Oncotarget* **2012**, *3*, 267–285. [CrossRef]

93. Kumagai, Y.; Nio-Kobayashi, J.; Ishida-Ishihara, S.; Tachibana, H.; Omori, R.; Enomoto, A.; Ishihara, S.; Haga, H. The intercellular expression of type-XVII collagen, laminin-332, and integrin-beta 1 promote contact following during the collective invasion of a cancer cell population. *Biochem. Biophys. Res. Commun.* **2019**, *514*, 1115–1121. [CrossRef] [PubMed]

94. Miyake, M.; Hori, S.; Morizawa, Y.; Tatsumi, Y.; Toritsuka, M.; Ohnishi, S.; Shimada, K.; Furuya, H.; Khadka, V.S.; Deng, Y.; et al. Collagen type IV alpha 1 (COL4A1) and collagen type XIII alpha 1 (COL13A1) produced in cancer cells promote tumor budding at the invasion front in human urothelial carcinoma of the bladder. *Oncotarget* **2017**, *8*, 36099–36114. [CrossRef] [PubMed]

95. Franjevic, A.; Pavicevic, R.; Bubanovic, G. ICTP in bone metastases of lung cancer. *Coll. Anthropol.* **2011**, *35*, 43–47.

96. Nurmenniemi, S.; Koivula, M.K.; Nyberg, P.; Tervahartiala, T.; Sorsa, T.; Mattila, P.S.; Salo, T.; Risteli, J. Type I and III collagen degradation products in serum predict patient survival in head and neck squamous cell carcinoma. *Oral Oncol.* **2012**, *48*, 136–140. [CrossRef] [PubMed]

97. Willumsen, N.; Bager, C.L.; Leeming, D.J.; Smith, V.; Christiansen, C.; Karsdal, M.A.; Dornan, D.; Bay-Jensen, A.C. Serum biomarkers reflecting specific tumor tissue remodeling processes are valuable diagnostic tools for lung cancer. *Cancer Med.* **2014**, *3*, 1136–1145. [CrossRef]

98. Ghassemi, H.; Hashemnia, M.; Mousavibahar, S.H.; Hosseini, H.M.; Mirhosseini, S.A. Positive Association of Matrix Proteins Alteration with TAZ and The Progression of High-Grade Bladder Cancer. *Cell J.* **2021**, *23*, 742–749.

99. Qin, L.P.; Zeng, J.P.; Shi, N.N.; Chen, L.; Wang, L. Application of weighted gene co-expression network analysis to explore the potential diagnostic biomarkers for colorectal cancer. *Mol. Med. Rep.* **2020**, *21*, 2533–2543. [CrossRef]

100. Zhu, Z.L.; Yang, G.Y.; Pang, Z.Z.; Liang, J.W.; Wang, W.Z.; Zhou, Y.L. Establishment of a regression model of bone metabolism markers for the diagnosis of bone metastases in lung cancer. *World J. Surg. Oncol.* **2021**, *19*, 27. [CrossRef]

101. Lipton, A.; Leitzel, K.; Ali, S.M.; Polimera, H.V.; Nagabhairu, V.; Marks, E.; Richardson, A.E.; Krecko, L.; Ali, A.; Koestler, W.; et al. High turnover of extracellular matrix reflected by specific protein fragments measured in serum is associated with poor outcomes in two metastatic breast cancer cohorts. *Int. J. Cancer* **2018**, *143*, 3027–3034. [CrossRef]

102. Ma, H.P.; Chang, H.L.; Bamodu, O.A.; Yadav, V.K.; Huang, T.Y.; Wu, A.T.H.; Yeh, C.T.; Tsai, S.H.; Lee, W.H. Collagen 1A1 (COL1A1) Is a Reliable Biomarker and Putative Therapeutic Target for Hepatocellular Carcinogenesis and Metastasis. *Cancers* **2019**, *11*, 786. [CrossRef]

103. Zulauf, N.; Bruggmann, D.; Groneberg, D.; Oremek, G.M. Expressiveness of Bone Markers in Breast Cancer with Bone Metastases. *Oncology* **2019**, *97*, 236–244. [CrossRef] [PubMed]

104. Rong, L.; Huang, W.; Tian, S.K.; Chi, X.B.; Zhao, P.; Liu, F.F. COL1A2 is a Novel Biomarker to Improve Clinical Prediction in Human Gastric Cancer: Integrating Bioinformatics and Meta-Analysis. *Pathol. Oncol. Res.* **2018**, *24*, 129–134. [CrossRef] [PubMed]

105. Narita, T.; Funahashi, H.; Satoh, Y.; Takagi, H. Procollagen type III N-peptide and type IV collagen 7S-domain in the sera of breast cancer patients. *Surg. Today* **1993**, *23*, 682–686. [CrossRef] [PubMed]

106. Chen, I.M.; Willumsen, N.; Dehlendorff, C.; Johansen, A.Z.; Jensen, B.V.; Hansen, C.P.; Hasselby, J.P.; Bojesen, S.E.; Pfeiffer, P.; Nielsen, S.E.; et al. Clinical value of serum hyaluronan and propeptide of type III collagen in patients with pancreatic cancer. *Int. J. Cancer* **2020**, *146*, 2913–2922. [CrossRef]

107. Mazurek, K.; Siemianowicz, K.; Likus, W.; Pierzchala, E.; Kwiatkowski, R.; Markowski, J. Collagen Type III Metabolism Evaluation in Patients with Malignant Head and Neck Cancer Treated with Radiotherapy. *BioMed Res. Int.* **2018**, *2018*, 8702605. [CrossRef]

108. Tomas, C.; Risteli, J.; Risteli, L.; Vuori, J.; Kauppila, A. Use of various epithelial tumor markers and a stromal marker in the assessment of cervical carcinoma. *Obstet. Gynecol.* **1991**, *77*, 566–572.

109. Akazawa, S.; Harada, A.; Futatsuki, K. Diagnostic values of type III Procollagen N-terminal peptide and combination assay of type III procollagen N-terminal peptide with CEA and CA 19-9 in gastric cancer. *Gan To Kagaku Ryoho. Cancer Chemother.* **1984**, *11*, 1434–1438.

110. Cracchiolo, B.M.; Hanauske-Abel, H.M.; Schwartz, P.E.; Chambers, J.T.; Holland, B.; Chambers, S.K. Procollagen-derived biomarkers in malignant ascites of ovarian cancer. Independent prognosticators for progression-free interval and survival. *Gynecol. Oncol.* **2002**, *87*, 24–33. [CrossRef]

111. Gabazza, E.C.; Taguchi, O.; Yamakami, T.; Machishi, M.; Ibata, H.; Tsutsui, K.; Suzuki, S. Coagulation-fibrinolysis system and markers of collagen metabolism in lung cancer. *Cancer* **1992**, *70*, 2631–2636. [CrossRef]

112. Attallah, A.M.; Albannan, M.S.; El-Deen, M.S.; Farid, K.; Khedr, F.M.; Attallah, K.A.; Abdallah, S.O. Diagnostic role of collagen-III and matrix metalloproteinase-1 for early detection of hepatocellular carcinoma. *Br. J. Biomed. Sci.* **2020**, *77*, 58–63. [CrossRef]

113. Gueugnon, F.; Leclercq, S.; Blanquart, C.; Sagan, C.; Cellerin, L.; Padieu, M.; Perigaud, C.; Scherpereel, A.; Gregoire, M. Identification of Novel Markers for the Diagnosis of Malignant Pleural Mesothelioma. *Am. J. Pathol.* **2011**, *178*, 1033–1042. [CrossRef]

114. Tang, M.; Liu, P.Q.; Wu, X.K.; Gong, J.; Weng, J.C.; Gao, G.Y.; Liu, Y.L.; Gan, L. COL3A1 and Its Related Molecules as Potential Biomarkers in the Development of Human Ewing's Sarcoma. *BioMed Res. Int.* **2021**, *2021*, 7453500. [CrossRef] [PubMed]

115. Kinoshita, J.; Fushida, S.; Harada, S.; Makino, I.; Nakamura, K.; Oyama, K.; Fujita, H.; Ninomiya, I.; Fujimura, T.; Kayahara, M.; et al. Type IV collagen levels are elevated in the serum of patients with peritoneal dissemination of gastric cancer. *Oncol. Lett.* **2010**, *1*, 989–994. [CrossRef]

116. Willumsen, N.; Bager, C.L.; Leeming, D.J.; Smith, V.; Karsdal, M.A.; Dornan, D.; Bay-Jensen, A.C. Extracellular matrix specific protein fingerprints measured in serum can separate pancreatic cancer patients from healthy controls. *BMC Cancer* **2013**, *13*, 554. [CrossRef]

117. Seko, Y.; Sumida, Y.; Tanaka, S.; Taketani, H.; Kanemasa, K.; Ishiba, H.; Okajima, A.; Nishimura, T.; Yamaguchi, K.; Moriguchi, M.; et al. Predictors of malignancies and overall mortality in Japanese patients with biopsy-proven non-alcoholic fatty liver disease. *Hepatol. Res.* **2015**, *45*, 728–738. [CrossRef]

118. Sumida, Y.; Yoneda, M.; Seko, Y.; Ishiba, H.; Hara, T.; Toyoda, H.; Yasuda, S.; Kumada, T.; Hayashi, H.; Japan Study Group of NAFLD (JSG-NAFLD); et al. Surveillance of Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease. *Diagnostics* **2020**, *10*, 579. [CrossRef]

119. Wang, H.B.; Liu, Z.D.; Li, A.; Wang, J.L.; Liu, J.T.; Liu, B.F.; Lian, X.Y.; Zhang, B.; Pang, B.; Liu, L.Y.; et al. COL4A1 as a novel oncogene associated with the clinical characteristics of malignancy predicts poor prognosis in glioma. *Exp. Therapeutic Med.* **2021**, *22*, 1224. [CrossRef]

120. Hiki, Y.; Iyama, K.-I.; Tsuruta, J.; Egami, H.; Kamio, T.; Suko, S.; Naito, I.; Sado, Y.; Ninomiya, Y.; Ogawa, M. Differential distribution of basement membrane type IV collagen alpha1(IV), alpha2(IV), alpha5(IV) and alpha6(IV) chains in colorectal epithelial tumors. *Pathol. Int.* **2002**, *52*, 224–233. [CrossRef]

121. Bager, C.L.; Willumsen, N.; Leeming, D.J.; Smith, V.; Karsdal, M.A.; Dornan, D.; Bay-Jensen, A.C. Collagen degradation products measured in serum can separate ovarian and breast cancer patients from healthy controls: A preliminary study. *Cancer Biomark.* **2015**, *15*, 783–788. [CrossRef] [PubMed]

122. Sameni, M.; Dosescu, J.; Yamada, K.M.; Sloane, B.F.; Cavallo-Medved, D. Functional live-cell imaging demonstrates that beta1-integrin promotes type IV collagen degradation by breast and prostate cancer cells. *Mol. Imaging* **2008**, *7*, 199–213. [CrossRef]

123. Ioachim, E.; Michael, M.; Stavropoulos, N.E.; Kitsiou, E.; Salmas, M.; Malamou-Mitsi, V. A clinicopathological study of the expression of extracellular matrix components in urothelial carcinoma. *BJU Int.* **2005**, *95*, 655–659. [CrossRef] [PubMed]

124. Chen, C.; Mendez, E.; Houck, J.; Fan, W.; Lohavanichbutr, P.; Doody, D.; Yueh, B.; Futran, N.D.; Upton, M.; Farwell, D.G.; et al. Gene expression profiling identifies genes predictive of oral squamous cell carcinoma. *Cancer Epidemiol. Biomark. Prevent.* **2008**, *17*, 2152–2162. [CrossRef] [PubMed]

125. Liu, Y.L.; Zhang, J.Y.; Chen, Y.; Sohel, H.; Ke, X.R.; Chen, J.Q.; Li, Y.X. The correlation and role analysis of COL4A1 and COL4A2 in hepatocarcinogenesis. *Aging-Us* **2020**, *12*, 204–223. [CrossRef] [PubMed]

126. Miyake, M.; Morizawa, Y.; Hori, S.; Tatsumi, Y.; Onishi, S.; Owari, T.; Iida, K.; Onishi, K.; Gotoh, D.; Nakai, Y.; et al. Diagnostic and prognostic role of urinary collagens in primary human bladder cancer. *Cancer Sci.* **2017**, *108*, 2221–2228. [CrossRef] [PubMed]

127. Yantiss, R.K.; Bosenberg, M.W.; Antonioli, D.A.; Odze, R.D. Utility of MMP-1, p53, E-cadherin, and collagen IV immunohistochemical stains in the differential diagnosis of adenomas with misplaced epithelium versus adenomas with invasive adenocarcinoma. *Am. J. Surg. Pathol.* **2002**, *26*, 206–215. [CrossRef] [PubMed]

128. Kayashima, H.; Maeda, T.; Harada, N.; Masuda, T.; Guntani, A.; Ito, S.; Matsuyama, A.; Hamatake, M.; Tsutsui, S.; Matsuda, H.; et al. Risk factors for incisional hernia after hepatic resection for hepatocellular carcinoma in patients with liver cirrhosis. *Surgery* **2015**, *158*, 1670–1676. [CrossRef]

129. Wang, J.; Jiang, Y.H.; Yang, P.Y.; Liu, F. Increased Collagen Type V alpha 2 (COL5A2) in Colorectal Cancer is Associated with Poor Prognosis and Tumor Progression. *Oncotargets Ther.* **2021**, *14*, 2991–3002. [CrossRef]

130. Ding, Y.L.; Sun, S.F.; Zhao, G.L. COL5A2 as a potential clinical biomarker for gastric cancer and renal metastasis. *Medicine* **2021**, *100*, e24561. [CrossRef]

131. Wu, M.; Sun, Q.; Mo, C.H.; Pang, J.S.; Hou, J.Y.; Pang, L.L.; Lu, H.P.; Dang, Y.W.; Fang, S.J.; Tang, D.; et al. Prospective molecular mechanism of COL5A1 in breast cancer based on a microarray, RNA sequencing and immunohistochemistry. *Oncol. Rep.* **2019**, *42*, 151–175. [CrossRef]

132. Balancin, M.L.; Teodoro, W.R.; Baldavira, C.M.; Prieto, T.G.; Farhat, C.; Velosa, A.P.; Souza, P.D.; Yaegashi, L.B.; Ab'Saber, A.M.; Takagaki, T.Y.; et al. Different histological patterns of type-V collagen levels confer a matrices-privileged tissue microenvironment for invasion in malignant tumors with prognostic value. *Pathol. Res. Pract.* **2020**, *216*, 153277. [CrossRef]

133. Willumsen, N.; Bager, C.; Karsdal, M.A. Matrix Metalloprotease Generated Fragments of Type VI Collagen Have Serum Biomarker Potential in Cancer—A Proof of Concept Study. *Transl. Oncol.* **2019**, *12*, 693–698. [CrossRef]

134. Kang, C.Y.; Wang, J.; Axell-House, D.; Soni, P.; Chu, M.L.; Chipitsyna, G.; Sarosiek, K.; Sendecki, J.; Hyslop, T.; Al-Zoubi, M.; et al. Clinical Significance of Serum COL6A3 in Pancreatic Ductal Adenocarcinoma. *J. Gastrointest. Surg.* **2014**, *18*, 7–15. [CrossRef]

135. Angenendt, L.; Mikesch, J.H.; Gorlich, D.; Busch, A.; Arnhold, I.; Rudack, C.; Hartmann, W.; Wardelmann, E.; Berdel, W.E.; Stenner, M.; et al. Stromal collagen type VI associates with features of malignancy and predicts poor prognosis in salivary gland cancer. *Cell. Oncol.* **2018**, *41*, 517–525. [CrossRef]

136. Arafat, H.; Lazar, M.; Salem, K.; Chipitsyna, G.; Gong, Q.K.; Pan, T.C.; Zhang, R.Z.; Yeo, C.J.; Chu, M.L. Tumor-specific expression and alternative splicing of the COL6A3 gene in pancreatic cancer. *Surgery* **2011**, *150*, 306–315. [CrossRef]

137. Fan, N.J.; Gao, C.F.; Wang, C.S.; Zhao, G.; Lv, J.J.; Wang, X.L.; Chu, G.H.; Yin, J.; Li, D.H.; Chen, X.; et al. Identification of the up-regulation of TP-alpha, collagen alpha-1(VI) chain, and S100A9 in esophageal squamous cell carcinoma by a proteomic method. *J. Proteom.* **2012**, *75*, 3977–3986. [CrossRef]

138. Wetzels, R.H.; Schaafsma, H.E.; Leigh, I.M.; Lane, E.B.; Troyanovsky, S.M.; Wagenaar, S.S.; Vooijs, G.P.; Ramaekers, F.C. Laminin and type VII collagen distribution in different types of human lung carcinoma: Correlation with expression of keratins 14, 16, 17 and 18. *Histopathology* **1992**, *20*, 295–303. [CrossRef]

139. Pourreyron, C.; Chen, M.; McGrath, J.A.; Salas-Alanis, J.C.; South, A.P.; Leigh, I.M. High levels of type VII collagen expression in recessive dystrophic epidermolysis bullosa cutaneous squamous cell carcinoma keratinocytes increases PI3K and MAPK signalling, cell migration and invasion. *Br. J. Dermatol.* **2014**, *170*, 1256–1265. [CrossRef]

140. Oh, S.E.; Oh, M.Y.; An, J.Y.; Lee, J.H.; Sohn, T.S.; Bae, J.M.; Choi, M.G.; Kim, K.M. Prognostic Value of Highly Expressed Type VII Collagen (COL7A1) in Patients with Gastric Cancer. *Pathol. Oncol. Res.* **2021**, *27*, 1609860. [CrossRef]

141. He, Z.H.; Deng, T.; Duan, X.L.; Zeng, G.H. Profiles of overall survival-related gene expression-based risk signature and their prognostic implications in clear cell renal cell carcinoma. *Biosci. Rep.* **2020**, *40*, Bsr20200492. [CrossRef]

142. Willumsen, N.; Jorgensen, L.N.; Karsdal, M.A. Vastatin (the NC1 domain of human type VIII collagen a1 chain) is linked to stromal reactivity and elevated in serum from patients with colorectal cancer. *Cancer Biol. Ther.* **2019**, *20*, 692–699. [CrossRef]

143. Peng, W.; Li, J.D.; Zeng, J.J.; Zou, X.P.; Tang, D.; Tang, W.; Rong, M.H.; Li, Y.; Dai, W.B.; Tang, Z.Q.; et al. Clinical value and potential mechanisms of COL8A1 upregulation in breast cancer: A comprehensive analysis. *Cancer Cell Int.* **2020**, *20*, 392. [CrossRef]

144. Shang, J.; Wang, F.; Chen, P.F.; Wang, X.B.; Ding, F.; Liu, S.; Zhao, Q. Co-expression Network Analysis Identified COL8A1 Is Associated with the Progression and Prognosis in Human Colon Adenocarcinoma. *Digest. Dis. Sci.* **2018**, *63*, 1219–1228. [CrossRef]

145. Zhang, D.W.; Zhu, H.F.; Harpaz, N. Overexpression of alpha 1 chain of type XI collagen (COL11A1) aids in the diagnosis of invasive carcinoma in endoscopically removed malignant colorectal polyps. *Pathol. Res. Pract.* **2016**, *212*, 545–548. [CrossRef]

146. Freire, J.; Dominguez-Hormaetxe, S.; Pereda, S.; De Juan, A.; Vega, A.; Simon, L.; Gomez-Roman, J. Collagen, type XI, alpha 1: An accurate marker for differential diagnosis of breast carcinoma invasiveness in core needle biopsies. *Pathol. Res. Pract.* **2014**, *210*, 879–884. [CrossRef]

147. Su, C.; Zhao, J.B.; Hong, X.Y.; Yang, S.J.; Jiang, Y.; Hou, J.J. Microarray-based analysis of COL11A1 and TWIST1 as important differentially-expressed pathogenic genes between left and right-sided colon cancer. *Mol. Med. Rep.* **2019**, *20*, 4202–4214. [CrossRef]

148. Zhao, Y.; Zhou, T.H.; Li, A.Q.; Yao, H.M.; He, F.; Wang, L.J.; Si, J.M. A Potential Role of Collagens Expression in Distinguishing Between Premalignant and Malignant Lesions in Stomach. *Anat. Rec.-Adv. Integr. Anat. Evol. Biol.* **2009**, *292*, 692–700. [CrossRef]

149. Wang, H.; Zhou, H.C.; Ni, H.; Shen, X.H. COL11A1-Driven Epithelial-Mesenchymal Transition and Sternness of Pancreatic Cancer Cells Induce Cell Migration and Invasion by Modulating the AKT/GSK-3 beta/Snail Pathway. *Biomolecules* **2022**, *12*, 391. [CrossRef]

150. Zheng, X.Y.; Liu, X.L.; Zheng, H.S.; Wang, H.N.; Hong, D.F. Integrated bioinformatics analysis identified COL11A1 as an immune infiltrates correlated prognosticator in pancreatic adenocarcinoma. *Int. Immunopharmacol.* **2021**, *90*, 106982. [CrossRef]

151. Garcia-Pravia, C.; Galvan, J.A.; Gutierrez-Corral, N.; Solar-Garcia, L.; Garcia-Perez, E.; Garcia-Ocana, M.; Del Amo-Iribarren, J.; Menendez-Rodriguez, P.; Garcia-Garcia, J.; de los Toyos, J.R.; et al. Overexpression of COL11A1 by Cancer-Associated Fibroblasts: Clinical Relevance of a Stromal Marker in Pancreatic Cancer. *PLoS ONE* **2013**, *8*, e78327.

152. Fuentes-Martinez, N.; Garcia-Pravia, C.; Garcia-Ocana, M.; Menendez-Rodriguez, P.; Del Amo, J.; Suarez-Fernandez, L.; Galvan, J.A.; Toyos, J.R.D.; Barneo, L. Overexpression of proCOL11A1 as a stromal marker of breast cancer. *Histol. Histopathol.* **2015**, *30*, 87–93.

153. Goto, R.; Nakamura, Y.; Takami, T.; Sanke, T.; Tozuka, Z. Quantitative LC-MS/MS Analysis of Proteins Involved in Metastasis of Breast Cancer. *PLoS ONE* **2015**, *10*, e0130760.

154. Husi, H.; MacDonald, A.; Skipworth, R.J.E.; Miller, J.; Cronshaw, A.; Greig, C.; Fearon, K.C.H.; Ross, J.A. Urinary diagnostic proteomic markers for dynapenia in cancer patients. *Biomed. Rep.* **2018**, *8*, 547–556. [CrossRef] [PubMed]

155. Franklin, O.; Ohlund, D.; Lundin, C.; Oman, M.; Naredi, P.; Wang, W.Z.; Sund, M. Combining conventional and stroma-derived tumour markers in pancreatic ductal adenocarcinoma. *Cancer Biomark.* **2015**, *15*, 1–10. [CrossRef]

156. Kantola, T.; Vayrynen, J.P.; Klintrup, K.; Makela, J.; Karppinen, S.M.; Pihlajaniemi, T.; Autio-Harmainen, H.; Karttunen, T.J.; Makinen, M.J.; Tuomisto, A. Serum endostatin levels are elevated in colorectal cancer and correlate with invasion and systemic inflammatory markers. *Br. J. Cancer* **2014**, *111*, 1605–1613. [CrossRef]

157. Xu, F.J.; Chang, K.; Ma, J.; Qu, Y.Y.; Xie, H.Y.; Dai, B.; Gan, H.L.; Zhang, H.L.; Shi, G.H.; Zhu, Y.; et al. The Oncogenic Role of COL23A1 in Clear Cell Renal Cell Carcinoma. *Sci. Rep.* **2017**, *7*, 9846. [CrossRef]

158. Angel, P.M.; Zambrzycki, S.C. Predictive value of collagen in cancer. *Adv. Cancer Res.* **2022**, *154*, 15–45. [PubMed]

159. Whatcott, C.J.; Diep, C.H.; Jiang, P.; Watanabe, A.; LoBello, J.; Sima, C.; Hostetter, G.; Shepard, H.M.; Von Hoff, D.D.; Han, H. Desmoplasia in Primary Tumors and Metastatic Lesions of Pancreatic Cancer. *Clin. Cancer Res.* **2015**, *21*, 3561–3568. [CrossRef]

160. Vasta, J.D.; Raines, R.T. Collagen Prolyl 4-Hydroxylase as a Therapeutic Target. *J. Med. Chem.* **2018**, *61*, 10403–10411. [CrossRef] [PubMed]

161. Qiu, S.; Fraser, S.P.; Pires, W.; Djamgoz, M.B.A. Anti-invasive effects of minoxidil on human breast cancer cells: Combination with ranolazine. *Clin. Exp. Metastasis* **2022**, *39*, 679–689. [CrossRef]

162. Qi, Y.F.; Xu, R. Roles of PLODs in Collagen Synthesis and Cancer Progression. *Front. Cell Dev. Biol.* **2018**, *6*, 66. [CrossRef]

163. Shi, W.Y.; Cao, C.; Liu, L. Interferon alpha Induces the Apoptosis of Cervical Cancer HeLa Cells by Activating both the Intrinsic Mitochondrial Pathway and Endoplasmic Reticulum Stress-Induced Pathway. *Int. J. Mol. Sci.* **2016**, *17*, 1832. [CrossRef]

164. Sun, X.H.; Cui, X.J.; Chen, X.H.; Jiang, X.G. Baicalein alleviated TGF beta 1-induced type I collagen production in lung fibroblasts via downregulation of connective tissue growth factor. *Biomed. Pharmacother.* **2020**, *131*, 110744. [CrossRef] [PubMed]

165. Tuli, H.S.; Aggarwal, V.; Kaur, J.; Aggarwal, D.; Parashar, G.; Parashar, N.C.; Tuorkey, M.; Kaur, G.; Savla, R.; Sak, K.; et al. Baicalein: A metabolite with promising antineoplastic activity. *Life Sci.* **2020**, *259*, 118183. [CrossRef]

166. Rishikof, D.C.; Ricupero, D.A.; Liu, H.; Goldstein, R.H. Phenylbutyrate decreases type I collagen production in human lung fibroblasts. *J. Cell. Biochem.* **2004**, *91*, 740–748. [CrossRef]

167. Xu, Y.W.; Zheng, S.B.; Chen, B.S.; Wen, Y.; Zhu, S.W. Sodium phenylbutyrate antagonizes prostate cancer through the induction of apoptosis and attenuation of cell viability and migration. *Oncotargets Ther.* **2016**, *9*, 2825–2833. [CrossRef]

168. Lee, J.-S.; Jin, H.Y.; Ko, J.M.; Kim, S.H.; Han, N.; Park, B.K.; Park, M.; Park, H.J.; Lee, J.A. Hyperammonemic Encephalopathy Mimicking Ornithine Transcarbamylase Deficiency in Fibrolamellar Hepatocellular Carcinoma: Successful Treatment with Continuous Venovenous Hemofiltration and Ammonia Scavengers. *Cancer Res. Treat.* **2021**, *53*, 283–288. [CrossRef]

169. Rubio, C.; Avendano-Ortiz, J.; Ruiz-Palomares, R.; Karaivanova, V.; Alberquilla, O.; Sanchez-Dominguez, R.; Casalvilla-Duenas, J.C.; Montalban-Hernandez, K.; Lodewijk, I.; Rodriguez-Izquierdo, M.; et al. Toward Tumor Fight and Tumor Microenvironment Remodeling: PBA Induces Cell Cycle Arrest and Reduces Tumor Hybrid Cells' Pluripotency in Bladder Cancer. *Cancers* **2022**, *14*, 287. [CrossRef]

170. Wang, Y.-Y.; Lee, K.-T.; Lim, M.C.; Choi, J.-H. TRPV1 Antagonist DWP05195 Induces ER Stress-Dependent Apoptosis through the ROS-p38-CHOP Pathway in Human Ovarian Cancer Cells. *Cancers* **2020**, *12*, 1702. [CrossRef]

171. Wu, Y.; Zhao, Y.; He, X.; He, Z.; Wang, T.; Wan, L.; Chen, L.; Yan, N. Hydroxypropyl-beta-cyclodextrin attenuates the epithelial-to-mesenchymal transition via endoplasmic reticulum stress in MDA-MB-231 breast cancer cells. *Mol. Med. Rep.* **2020**, *21*, 249–257.

172. Stefanovic, B.; Manojlovic, Z.; Vied, C.; Badger, C.D.; Stefanovic, L. Discovery and evaluation of inhibitor of LARP6 as specific antifibrotic compound. *Sci. Rep.* **2019**, *9*, 326. [CrossRef]

173. Agarwal, S.; Behring, M.; Kim, H.G.; Bajpai, P.; Chakravarthi, B.; Gupta, N.; Elkholy, A.; Al Diffalha, S.; Varambally, S.; Manne, U. Targeting P4HA1 with a Small Molecule Inhibitor in a Colorectal Cancer PDX Model. *Transl. Oncol.* **2020**, *13*, 100754. [CrossRef]

174. Gilkes, D.M.; Chaturvedi, P.; Bajpai, S.; Wong, C.C.; Wei, H.; Pitcairn, S.; Hubbi, M.E.; Wirtz, D.; Semenza, G.L. Collagen Prolyl Hydroxylases Are Essential for Breast Cancer Metastasis. *Cancer Res.* **2013**, *73*, 3285–3296. [CrossRef]

175. Chen, I.S.; Chou, C.-T.; Liu, Y.-Y.; Yu, C.-C.; Liang, W.-Z.; Kuo, C.-C.; Shieh, P.; Kuo, D.-H.; Chen, F.-A.; Jan, C.-R. The investigation of minoxidil-induced Ca2+ (i) rises and non-Ca2+-triggered cell death in PC3 human prostate cancer cells. *J. Recept. Signal Transduct.* **2017**, *37*, 1–7. [CrossRef]

176. Fukushiro-Lopes, D.; Jain, M.; Khalid, M.; Hegel, A.; Gentile, S. Potassium channel activator minoxidil (Rogaine) as a novel single-agent or combination therapy in ovarian cancer. *Clin. Cancer Res.* **2018**, *24*, 66–67. [CrossRef]

177. Ito, S.; Ogawa, K.; Takeuchi, K.; Takagi, M.; Yoshida, M.; Hirokawa, T.; Hirayama, S.; Shin-ya, K.; Shimada, I.; Doi, T.; et al. A small-molecule compound inhibits a collagen-specific molecular chaperone and could represent a potential remedy for fibrosis. *J. Biol. Chem.* **2017**, *292*, 20076–20085. [CrossRef]

178. Miyamura, T.; Sakamoto, N.; Kakugawa, T.; Taniguchi, H.; Akiyama, Y.; Okuno, D.; Moriyama, S.; Hara, A.; Kido, T.; Ishimoto, H.; et al. Small molecule inhibitor of HSP47 prevents pro-fibrotic mechanisms of fibroblasts in vitro. *Biochem. Biophys. Res. Commun.* **2020**, *530*, 561–565. [CrossRef]

179. Leung, L.; Niculescu-Duyaz, D.; Smithen, D.; Lopes, F.; Callens, C.; McLeary, R.; Saturno, G.; Davies, L.; Aljarah, M.; Brown, M.; et al. Anti-metastatic Inhibitors of Lysyl Oxidase (LOX): Design and Structure-Activity Relationships. *J. Med. Chem.* **2019**, *62*, 5863–5884. [CrossRef]

180. Wang, T.-H.; Hsia, S.-M.; Shieh, T.-M. Lysyl Oxidase and the Tumor Microenvironment. *Int. J. Mol. Sci.* **2017**, *18*, 62. [CrossRef]

181. Kelley, R.K.; Gane, E.; Assenat, E.; Siebler, J.; Galle, P.R.; Merle, P.; Hourmand, I.O.; Cleverly, A.; Zhao, Y.; Gueorguieva, I.; et al. A Phase 2 Study of Galunisertib (TGF-β1 Receptor Type I Inhibitor) and Sorafenib in Patients with Advanced Hepatocellular Carcinoma. *Clin. Transl. Gastroenterol.* **2019**, *10*, e00056. [CrossRef] [PubMed]

182. Wu, Y.-H.; Chou, C.-Y. Collagen XI Alpha 1 Chain, a Novel Therapeutic Target for Cancer Treatment. *Front. Oncol.* **2022**, *12*, 925165. [CrossRef]

183. Chen, J.; Li, S.; Liu, X.; Liu, S.; Xiao, C.; Zhang, Z.; Li, S.; Li, Z.; Yang, X. Transforming growth factor-beta blockade modulates tumor mechanical microenvironments for enhanced antitumor efficacy of photodynamic therapy. *Nanoscale* **2021**, *13*, 9989–10001. [CrossRef] [PubMed]

184. Wang, Y.; Gao, Z.; Du, X.; Chen, S.; Zhang, W.; Wang, J.; Li, H.; He, X.; Cao, J.; Wang, J. Co-inhibition of the TGF-beta pathway and the PD-L1 checkpoint by pH-responsive clustered nanoparticles for pancreatic cancer microenvironment regulation and anti-tumor immunotherapy. *Biomater. Sci.* **2020**, *8*, 5121–5132. [CrossRef] [PubMed]

185. Zhang, Q.; Hou, X.; Evans, B.J.; VanBlaricom, J.L.; Weroha, S.J.; Cliby, W.A. LY2157299 Monohydrate, a TGF-beta R1 Inhibitor, Suppresses Tumor Growth and Ascites Development in Ovarian Cancer. *Cancers* **2018**, *10*, 260. [CrossRef] [PubMed]

186. Wu, Y.H.; Huang, Y.F.; Chen, C.C.; Chou, C.Y. Akt inhibitor SC66 promotes cell sensitivity to cisplatin in chemoresistant ovarian cancer cells through inhibition of COL11A1 expression. *Cell Death Dis.* **2019**, *10*, 322. [CrossRef]

187. Cai, X.; Hu, B.; Liu, S.; Liu, M.; Huang, Y.; Lei, P.; Zhang, Z.; He, Z.; Zhang, L.; Huang, R. Overexpression of close homolog of L1 enhances the chemosensitivity of lung cancer cells via inhibition of the Akt pathway. *Oncol. Lett.* **2020**, *20*, 111. [CrossRef]

188. Chen, W.; Zhao, S.; Yu, W.; Rao, T.; Ruan, Y.; Zhu, S.; Xia, Y.; Song, H.; Cheng, F. SC66 inhibits the proliferation and induces apoptosis of human bladder cancer cells by targeting the AKT/beta-catenin pathway. *J. Cell. Mol. Med.* **2021**, *25*, 10684–10697. [CrossRef]

189. Liu, Y.; Huang, Y.; Ding, J.; Liu, N.; Peng, S.; Wang, J.; Wang, F.; Zhang, Y. Targeting Akt by SC66 triggers GSK-3 mediated apoptosis in colon cancer therapy. *Cancer Cell Int.* **2019**, *19*, 124. [CrossRef]

190. Bourgot, I.; Primac, I.; Louis, T.; Noel, A.; Maquoi, E. Reciprocal Interplay Between Fibrillar Collagens and Collagen-Binding Integrins: Implications in Cancer Progression and Metastasis. *Front. Oncol.* **2020**, *10*, 1488. [CrossRef]

191. Ivaska, J.; Heino, J. Adhesion receptors and cell invasion: Mechanisms of integrin-guided degradation of extracellular matrix. *Cell. Mol. Life Sci. CMLS* **2000**, *57*, 16–24. [CrossRef]

192. Coopman, P.J.; Thomas, D.M.; Gehlsen, K.R.; Mueller, S.C. Integrin alpha 3 beta 1 participates in the phagocytosis of extracellular matrix molecules by human breast cancer cells. *Mol. Biol. Cell* **1996**, *7*, 1789–1804. [CrossRef]

193. Feng, X.; Jin, L. Relationship between integrin alpha v beta 3 and alpha 6 beta 1 expression levels and clinicopathological characteristics of cervical cancer. *Trop. J. Pharm. Res.* **2020**, *19*, 2323–2328.

194. Gupta, S.K.; Oommen, S.; Aubry, M.C.; Williams, B.P.; Vlahakis, N.E. Integrin alpha 9 beta 1 promotes malignant tumor growth and metastasis by potentiating epithelial-mesenchymal transition. *Oncogene* **2013**, *32*, 141–150. [CrossRef] [PubMed]

195. Rentala, S.; Yalavarthy, P.D.; Mangamoori, L.N. alpha 1 and beta 1 integrins enhance the homing and differentiation of cultured prostate cancer stem cells. *Asian J. Androl.* **2010**, *12*, 548–555. [CrossRef]

196. Sawai, H.; Okada, Y.; Funahashi, H.; Matsuo, Y.; Takahashi, H.; Takeyama, H.; Manabe, T. Interleukin-1alpha enhances the aggressive behavior of pancreatic cancer cells by regulating the alpha6beta1-integrin and urokinase plasminogen activator receptor expression. *BMC Cell Biol.* **2006**, *7*, 8. [CrossRef]

197. Scalici, J.M.; Harrer, C.; Allen, A.; Jazaeri, A.; Atkins, K.A.; McLachlan, K.R.; Slack-Davis, J.K. Inhibition of alpha 4 beta 1 integrin increases ovarian cancer response to carboplatin. *Gynecol. Oncol.* **2014**, *132*, 455–461. [CrossRef]

198. Subbaram, S.; DiPersio, C.M. Integrin alpha 3 beta 1 as a breast cancer target. *Expert Opin. Ther. Targets* **2011**, *15*, 1197–1210. [CrossRef]

199. Wang, H.-Y.; Chen, Z.; Wang, Z.-H.; Wang, H.; Huang, L.-M. Prognostic Significance of alpha 5 beta 1-integrin Expression in Cervical Cancer. *Asian Pac. J. Cancer Prevent.* **2013**, *14*, 3891–3895. [CrossRef]

200. Zhou, M.; Niu, J.; Wang, J.; Gao, H.; Shahbaz, M.; Niu, Z.; Li, Z.; Zou, X.; Liang, B. Integrin alpha v beta 8 serves as a Novel Marker of Poor Prognosis in Colon Carcinoma and Regulates Cell Invasiveness through the Activation of TGF-beta 1. *J. Cancer* **2020**, *11*, 3803–3815. [CrossRef]

201. Hirata, E.; Girotti, M.R.; Viros, A.; Hooper, S.; Spencer-Dene, B.; Matsuda, M.; Larkin, J.; Marais, R.; Sahai, E. Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin β1/FAK signaling. *Cancer Cell* **2015**, *27*, 574–588. [CrossRef]

202. Hanker, A.B.; Estrada, M.V.; Bianchini, G.; Moore, P.D.; Zhao, J.; Cheng, F.; Koch, J.P.; Gianni, L.; Tyson, D.R.; Sánchez, V.; et al. Extracellular Matrix/Integrin Signaling Promotes Resistance to Combined Inhibition of HER2 and PI3K in HER2(+) Breast Cancer. *Cancer Res.* **2017**, *77*, 3280–3292. [CrossRef]

203. Lasinska, I.; Mackiewicz, J. Integrins as A New Target for Cancer Treatment. *Anti-Cancer Agents Med. Chem.* **2019**, *19*, 580–586. [CrossRef] [PubMed]

204. Lautenschlaeger, T.; Perry, J.; Peereboom, D.; Li, B.; Ibrahim, A.; Huebner, A.; Meng, W.; White, J.; Chakravarti, A. In vitro study of combined cilengitide and radiation treatment in breast cancer cell lines. *Radiat. Oncol.* **2013**, *8*, 246. [CrossRef]

205. Reardon, D.A.; Cheresh, D. Cilengitide: A prototypic integrin inhibitor for the treatment of glioblastoma and other malignancies. *Genes Cancer* **2011**, *2*, 1159–1165. [CrossRef]

206. Hamidi, H.; Ivaska, J. Every step of the way: Integrins in cancer progression and metastasis. *Nat. Rev. Cancer* **2018**, *18*, 533–548. [CrossRef]

207. Massabeau, C.; Khalifa, J.; Filleron, T.; Modesto, A.; Bigay-Gamé, L.; Plat, G.; Dierickx, L.; Aziza, R.; Rouquette, I.; Gomez-Roca, C.; et al. Continuous Infusion of Cilengitide Plus Chemoradiotherapy for Patients With Stage III Non-Small-cell Lung Cancer: A Phase I Study. *Clin. Lung Cancer* **2018**, *19*, e277–e285. [CrossRef]

208. Akhtar, B.; Muhammad, F.; Sharif, A.; Anwar, M.I. Mechanistic insights of snake venom disintegrins in cancer treatment. *Eur. J. Pharmacol.* **2021**, *899*, 174022. [CrossRef]

209. Khanna, D.; Tashkin, D.P.; Wells, A.U.; Seibold, J.R.; Wax, S.; Vazquez-Mateo, C.; Fleuranceau-Morel, P.; Damian, D.; Denton, C.P. STRATUS: A Phase II Study of Abituzumab in Patients With Systemic Sclerosis-associated Interstitial Lung Disease. *J. Rheumatol.* **2021**, *48*, 1295–1298. [CrossRef]

210. Zhu, J.J.; Cheng, H.; Wang, L.; Xu, W.D.; Wang, J.Q.; Han, Q.; Lee, J.H.; Du, L.Y.; Lyu, J.X. Discoidin domain receptor 1 promotes lung adenocarcinoma migration via the AKT/snail signaling axis. *Mol. Biol. Rep.* **2022**, *49*, 7275–7286. [CrossRef]

211. Matada, G.S.P.; Das, A.; Dhiwar, P.S.; Ghara, A. DDR1 and DDR2: A review on signaling pathway and small molecule inhibitors as an anticancer agent. *Med. Chem. Res.* **2021**, *30*, 535–551. [CrossRef]

212. Gao, Y.; Zhou, J.L.; Li, J. Discoidin domain receptors orchestrate cancer progression: A focus on cancer therapies. *Cancer Sci.* **2021**, *112*, 962–969. [CrossRef]

213. Deng, J.Y.; Kang, Y.; Cheng, C.C.; Li, X.Q.; Dai, B.B.; Katz, M.H.; Men, T.; Kim, M.P.; Koay, E.A.; Huang, H.C.; et al. DDR1-induced neutrophil extracellular traps drive pancreatic cancer metastasis. *JCI Insight* **2021**, *6*, e146133. [CrossRef]

214. Huo, Y.M.; Yang, M.W.; Liu, W.; Yang, J.Y.; Fu, X.L.; Liu, D.J.; Li, J.; Zhang, J.F.; Hua, R.; Sun, Y.W. High expression of DDR1 is associated with the poor prognosis in Chinese patients with pancreatic ductal adenocarcinoma. *J. Exp. Clin. Cancer Res.* **2015**, *34*, 88. [CrossRef]

215. Xie, X.; He, H.C.; Zhang, N.; Wang, X.J.; Rui, W.B.; Xu, D.F.; Zhu, Y. Overexpression of DDR1 Promotes Migration, Invasion, Though EMT-Related Molecule Expression and COL4A1/DDR1/MMP-2 Signaling Axis. *Technol. Cancer Res. Treat.* **2020**, *19*, 1533033820973277. [CrossRef]

216. Jeitany, M.; Leroy, C.; Tosti, P.; Lafitte, M.; Le Guet, J.; Simon, V.; Bonenfant, D.; Robert, B.; Grillet, F.; Mollevi, C.; et al. Inhibition of DDR1-BCR signalling by nilotinib as a new therapeutic strategy for metastatic colorectal cancer. *EMBO Mol. Med.* **2018**, *10*, e7918. [CrossRef]

217. Henriet, E.; Sala, M.; Abou Hammoud, A.; Tuariihionoa, A.; Di Martino, J.; Ros, M.; Saltel, F. Multitasking discoidin domain receptors are involved in several and specific hallmarks of cancer. *Cell Adhes. Migr.* **2018**, *12*, 363–377. [CrossRef]

218. Lu, Q.-P.; Chen, W.-D.; Peng, J.-R.; Xu, Y.-D.; Cai, Q.; Feng, G.-K.; Ding, K.; Zhu, X.-F.; Guan, Z. Antitumor activity of 7RH, a discoidin domain receptor 1 inhibitor, alone or in combination with dasatinib exhibits antitumor effects in nasopharyngeal carcinoma cells. *Oncol. Lett.* **2016**, *12*, 3598–3608. [CrossRef] [PubMed]

219. Alhalabi, O.T.; Fletcher, M.N.C.; Hielscher, T.; Kessler, T.; Lokumcu, T.; Baumgartner, U.; Wittmann, E.; Schlue, S.; Goettmann, M.; Rahman, S.; et al. A novel patient stratification strategy to enhance the therapeutic efficacy of dasatinib in glioblastoma. *Neuro-Oncology* **2022**, *24*, 39–51. [CrossRef]

220. Araujo, J.C.; Poblenz, A.; Corn, P.G.; Parikh, N.U.; Starbuck, M.W.; Thompson, J.T.; Lee, F.; Logothetis, C.J.; Darnay, B.G. Dasatinib inhibits both osteoclast activation and prostate cancer PC-3 cell-induced osteoclast formation. *Cancer Biol. Ther.* **2009**, *8*, 2153–2159. [CrossRef]

221. Johnson, F.M.; Saigal, B.; Talpaz, M.; Donato, N.J. Dasatinib (BMS-354825) tyrosine kinase inhibitor suppresses invasion and induces cell cycle arrest and apoptosis of head and neck squamous cell carcinoma and non-small cell lung cancer cells. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2005**, *11 Pt 1*, 6924–6932. [CrossRef]

222. Kurashige, J.; Hasegawa, T.; Niida, A.; Sugimachi, K.; Deng, N.; Mima, K.; Uchi, R.; Sawada, G.; Takahashi, Y.; Eguchi, H.; et al. Integrated Molecular Profiling of Human Gastric Cancer Identifies DDR2 as a Potential Regulator of Peritoneal Dissemination. *Sci. Rep.* **2016**, *6*, 22371. [CrossRef]

223. Somlo, G.; Atzori, F.; Strauss, L.C.; Geese, W.J.; Specht, J.M.; Gradishar, W.J.; Rybicki, A.; Sy, O.; Vahdat, L.T.; Cortes, J. Dasatinib plus Capecitabine for Advanced Breast Cancer: Safety and Efficacy in Phase I Study CA180004. *Clin. Cancer Res.* **2013**, *19*, 1884–1893. [CrossRef] [PubMed]

224. Ohashi, K.; Pao, W. A New Target for Therapy in Squamous Cell Carcinoma of the Lung. *Cancer Discov.* **2011**, *1*, 23–24. [CrossRef] [PubMed]

225. Leroy, C.; Robert, B.; Simon, V.; Roche, S. The Abl tyrosine kinase inhibitor Nilotinib inhibits invasive properties of colon cancer cells by targeting the discoidin domain receptor 1. *EJC Suppl.* **2010**, *8*, 113. [CrossRef]

226. Sirvent, A.; Lafitte, M.; Roche, S. DDR1 inhibition as a new therapeutic strategy for colorectal cancer. *Mol. Cell. Oncol.* **2018**, *5*, e1465882. [CrossRef] [PubMed]

227. Ahmed, N.; Vengalasetti, Y.; Haslam, A.; Prasad, V. Association of Adjuvant or Metastatic Setting with Discontinuation of Cancer Drugs in Clinical Trials. *Jama Netw. Open* **2022**, *5*, e2212327. [CrossRef]

228. Italiano, A. Next questions for the medical treatment of gastrointestinal stromal tumor. *Curr. Opin. Oncol.* **2022**, *34*, 348–353. [CrossRef]

229. Nazzal, M.; Sur, S.; Steele, R.; Khatun, M.; Patra, T.; Phillips, N.; Long, J.; Ray, R.; Ray, R.B. Establishment of a Patient-Derived Xenograft Tumor from Hepatitis C-Associated Liver Cancer and Evaluation of Imatinib Treatment Efficacy. *Hepatology* **2020**, *72*, 379–388. [CrossRef]

230. Puri, S.; Kaur, G.; Piplani, H.; Sanyal, S.N.; Vaish, V. Imatinib modulates pro-inflammatory microenvironment with angiostatic effects in experimental lung carcinogenesis. *Inflammopharmacology* **2020**, *28*, 231–252. [CrossRef]

231. Copland, M.; Slade, D.; McIlroy, G.; Horne, G.; Byrne, J.L.; Rothwell, K.; Brock, K.; De Lavallade, H.; Craddock, C.; Clark, R.E.; et al. Ponatinib with fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor chemotherapy for patients with blast-phase chronic myeloid leukaemia (MATCHPOINT): A single-arm, multicentre, phase 1/2 trial. *Lancet Haematol.* **2022**, *9*, E121–E132. [CrossRef]

232. Canning, P.; Tan, L.; Chu, K.; Lee, S.W.; Gray, N.S.; Bullock, A.N. Structural Mechanisms Determining Inhibition of the Collagen Receptor DDR1 by Selective and Multi-Targeted Type II Kinase Inhibitors. *J. Mol. Biol.* **2014**, *426*, 2457–2470. [CrossRef]

233. Tao, Y.; Wang, R.; Lai, Q.; Wu, M.; Wang, Y.; Jiang, X.; Zeng, L.; Zhou, S.; Li, Z.; Yang, T.; et al. Targeting of DDR1 with antibody-drug conjugates has antitumor effects in a mouse model of colon carcinoma. *Mol. Oncol.* **2019**, *13*, 1855–1873. [CrossRef] [PubMed]

234. Grither, W.R.; Longmore, G.D. Inhibition of tumor-microenvironment interaction and tumor invasion by small-molecule allosteric inhibitor of DDR2 extracellular domain. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E7786–E7794. [CrossRef] [PubMed]

235. Rammal, H.; Saby, C.; Magnien, K.; Van-Gulick, L.; Gamotel, P.; Buache, E.; El Btaouri, H.; Jeannesson, P.; Morjani, H. Discoidin Domain Receptors: Potential Actors and Targets in Cancer. *Front. Pharmacol.* **2016**, *7*, 55. [CrossRef]

236. Fowler, A.J.; Hebron, M.; Balaraman, K.; Shi, W.; Missner, A.A.; Greenzaid, J.D.; Chiu, T.L.; Ullman, C.; Weatherdon, E.; Duka, V.; et al. Discoidin Domain Receptor 1 is a therapeutic target for neurodegenerative diseases. *Hum. Mol. Genet.* **2020**, *29*, 2882–2898. [CrossRef] [PubMed]

237. Fowler, A.J.; Hebron, M.; Missner, A.A.; Wang, R.; Gao, X.; Kurd-Misto, B.T.; Liu, X.; Moussa, C.E.H. Multikinase Abl/DDR/Src Inhibition Produces Optimal Effects for Tyrosine Kinase Inhibition in Neurodegeneration. *Drugs R D* **2019**, *19*, 149–166. [CrossRef]

238. Richters, A.; Nguyen, H.D.; Trang, P.; Simard, J.R.; Gruetter, C.; Engel, J.; Rauh, D. Identification of Type II and III DDR2 Inhibitors. *J. Med. Chem.* **2014**, *57*, 4252–4262. [CrossRef]

239. Dai, W.; Liu, S.; Wang, S.; Zhao, L.; Yang, X.; Zhou, J.; Wang, Y.; Zhang, J.; Zhang, P.; Ding, K.; et al. Activation of transmembrane receptor tyrosine kinase DDR1-STAT3 cascade by extracellular matrix remodeling promotes liver metastatic colonization in uveal melanoma. *Signal Transduct. Target. Ther.* **2021**, *6*, 176. [CrossRef]

240. Yao, J.; Li, G.; Jiao, Y.; Zheng, Y.; Liu, Y.; Wang, G.; Zhou, L.; Zhang, H.; Zhang, X.; Shuai, J.; et al. Biological gel-based microchamber array for tumor cell proliferation and migration studies in well-controlled biochemical gradients. *Lab Chip* **2021**, *21*, 3004–3018. [CrossRef]

241. Aguilera, K.Y.; Huang, H.; Du, W.; Hagopian, M.M.; Wang, Z.; Hinz, S.; Hwang, T.H.; Wang, H.; Fleming, J.B.; Castrillon, D.H.; et al. Inhibition of Discoidin Domain Receptor 1 Reduces Collagen-mediated Tumorigenicity in Pancreatic Ductal Adenocarcinoma. *Mol. Cancer Ther.* **2017**, *16*, 2473–2485. [CrossRef]

242. Shariati, M.; Evans, K.W.; Zheng, X.; Bristow, C.A.; Ng, P.K.-S.; Rizvi, Y.Q.; Tapia, C.; Yang, F.; Carugo, A.; Heffernan, T.P.; et al. Combined inhibition of DDR1 and CDK4/6 induces synergistic effects in ER-positive, HER2-negative breast cancer with PIK3CA/AKT1 mutations. *Oncogene* **2021**, *40*, 4425–4439. [CrossRef]

243. Wei, Z.-W.; Zhang, C.-H.; He, Y. 7rh, a novel selective discoidin domain receptor 1 (DDR1) inhibitor, enhances 5-fluorouracil response in gastric cancer. *Ann. Oncol.* **2017**, *28*, iii18. [CrossRef]

244. de Moura, C.R.; Battistella, M.; Sohail, A.; Caudron, A.; Feugeas, J.P.; Podgorniak, M.-P.; Pages, C.; Dorval, S.M.; Marco, O.; Menashi, S.; et al. Discoidin domain receptors: A promising target in melanoma. *Pigment Cell Melanoma Res.* **2019**, *32*, 697–707.

245. Romayor, I.; Badiola, I.; Benedicto, A.; Marquez, J.; Herrero, A.; Arteta, B.; Olaso, E. Silencing of sinusoidal DDR1 reduces murine liver metastasis by colon carcinoma. *Sci. Rep.* **2020**, *10*, 18398. [CrossRef]

246. Kim, H.-G.; Tan, L.; Weisberg, E.L.; Liu, F.; Canning, P.; Choi, H.G.; Ezell, S.A.; Wu, H.; Zhao, Z.; Wang, J.; et al. Discovery of a Potent and Selective DDR1 Receptor Tyrosine Kinase Inhibitor. *ACS Chem. Biol.* **2013**, *8*, 2145–2150. [CrossRef] [PubMed]

247. Li, T.; Zhang, H.; Wang, Z.; Gao, S.; Zhang, X.; Zhu, H.; Wang, N.; Li, H. The regulation of autophagy by the miR-199a-5p/p62 axis was a potential mechanism of small cell lung cancer cisplatin resistance. *Cancer Cell Int.* **2022**, *22*, 120. [CrossRef]

248. Yang, X.; Zheng, Y.; Tan, J.; Tian, R.; Shen, P.; Cai, W.; Liao, H. MiR-199a-5p-HIF-1 alpha-STAT3 Positive Feedback Loop Contributes to the Progression of Non-Small Cell Lung Cancer. *Front. Cell Dev. Biol.* **2021**, *8*, 620615. [CrossRef]

249. Hu, Y.; Liu, J.; Jiang, B.; Chen, J.; Fu, Z.; Bai, F.; Jiang, J.; Tang, Z. MiR-199a-5p Loss Up-Regulated DDR1 Aggravated Colorectal Cancer by Activating Epithelial-to-Mesenchymal Transition Related Signaling. *Digest. Dis. Sci.* **2014**, *59*, 2163–2172. [CrossRef]

250. Krazinski, B.E.; Kiewisz, J.; Sliwinska-Jewsiewicka, A.; Kowalczyk, A.E.; Grzegrzolka, J.; Godlewski, J.; Kwiatkowski, P.; Dziegiel, P.; Kmiec, Z. Altered Expression of DDR1 in Clear Cell Renal Cell Carcinoma Correlates With miR-199a/b-5p and Patients' Outcome. *Cancer Genom. Proteom.* **2019**, *16*, 179–193. [CrossRef]

251. Ilbeigi, S.; Naeimzadeh, Y.; Davoodabadi Farahani, M.; Rafi Monjezi, M.; Dastsooz, H.; Daraei, A.; Farahani, F.; Dastgheib, A.; Mansoori, Y.; Tabei, S.M.B. Clinical values of two estrogen receptor signaling targeted lncRNAs in invasive ductal breast carcinoma. *Klin. Onkol. Cas. Ces. A Slov. Onkol. Spol.* **2021**, *34*, 382–391. [CrossRef]

252. Najafi, M.; Farhood, B.; Mortezaee, K. Extracellular matrix (ECM) stiffness and degradation as cancer drivers. *J. Cell. Biochem.* **2019**, *120*, 2782–2790. [CrossRef] [PubMed]

253. Li, G.; Tao, T.; Deng, D.; Zhang, S.; Chao, Y.; Dai, Y.; Li, Y.; Tao, R.; Yuan, S.; Liu, Z.; et al. Collagen-targeted tumor-specific transepithelial penetration enhancer mediated intravesical chemoimmunotherapy for non-muscle-invasive bladder cancer. *Biomaterials* **2022**, *283*, 121422. [CrossRef] [PubMed]

254. Chauhan, V.P.; Martin, J.D.; Liu, H.; Lacorre, D.A.; Jain, S.R.; Kozin, S.V.; Stylianopoulos, T.; Mousa, A.S.; Han, X.X.; Adstamongkonkul, P.; et al. Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels. *Nat. Commun.* **2013**, *4*, 2516.

255. Kasi, A.; Allen, J.; Mehta, K.; Dandawate, P.; Saha, S.; Bossmann, S.; Anant, S.; Sun, W. Association of losartan with outcomes in metastatic pancreatic cancer patients treated with chemotherapy. *J. Clin. Transl. Res.* **2021**, *7*, 257–262.

256. Zhao, Y.; Cao, J.; Melamed, A.; Worley, M.; Gockley, A.; Jones, D.; Nia, H.T.; Zhang, Y.; Stylianopoulos, T.; Kumar, A.S.; et al. Losartan treatment enhances chemotherapy efficacy and reduces ascites in ovarian cancer models by normalizing the tumor stroma. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 2210–2219. [CrossRef]

257. Cardinale, D.; Sandri, M.T.; Colombo, A.; Salvatici, M.; Tedeschi, I.; Bacchiani, G.; Beggiato, M.; Meroni, C.A.; Civelli, M.; Lamantia, G.; et al. Prevention of Atrial Fibrillation in High-risk Patients Undergoing Lung Cancer Surgery the PRESAGE Trial. *Ann. Surg.* **2016**, *264*, 244–251. [CrossRef] [PubMed]

258. Choi, C.H.; Park, Y.-A.; Choi, J.-J.; Song, T.; Song, S.Y.; Lee, Y.-Y.; Lee, J.-W.; Kim, T.-J.; Kim, B.-G.; Bae, D.-S. Angiotensin II type I receptor and miR-155 in endometrial cancers: Synergistic antiproliferative effects of anti-miR-155 and losartan on endometrial cancer cells. *Gynecol. Oncol.* **2012**, *126*, 124–131. [CrossRef] [PubMed]

259. Hashemzehi, M.; Rahmani, F.; Khoshakhlagh, M.; Avan, A.; Asgharzadeh, F.; Barneh, F.; Moradi-Marjaneh, R.; Soleimani, A.; Fiuji, H.; Ferns, G.A.; et al. Angiotensin Receptor Blocker Losartan Inhibits Tumor Growth of Colorectal Cancer. *EXCLI J.* **2021**, *20*, 506–521. [PubMed]

260. Yazdannejat, H.; Hosseinimehr, S.J.; Ghasemi, A.; Pourfallah, T.A.; Rafiei, A. Losartan sensitizes selectively prostate cancer cell to ionizing radiation. *Cell. Mol. Biol.* **2016**, *62*, 30–33.

261. Zhao, Q.; He, X.; Qin, X.; Liu, Y.; Jiang, H.; Wang, J.; Wu, S.; Zhou, R.; Yu, C.; Liu, S.; et al. Enhanced Therapeutic Efficacy of Combining Losartan and Chemo-Immunotherapy for Triple Negative Breast Cancer. *Front. Immunol.* **2022**, *13*, 938439. [CrossRef]

262. Miwa, S.; Yamamoto, N.; Hayashi, K.; Takeuchi, A.; Igarashi, K.; Tsuchiya, H. Therapeutic Targets and Emerging Treatments in Advanced Chondrosarcoma. *Int. J. Mol. Sci.* **2022**, *23*, 1096. [CrossRef]

263. Romanchikova, N.; Trapencieris, P.; Zemitis, J.; Turks, M. A novel matrix metalloproteinase-2 inhibitor triazolylmethyl aziridine reduces melanoma cell invasion, angiogenesis and targets ERK1/2 phosphorylation. *J. Enzym. Inhib. Med. Chem.* **2014**, *29*, 765–772. [CrossRef] [PubMed]