Cancer Letters 582 (2024) 216583

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-Review

The post-chemotherapy changes of tumor physical microenvironment: Targeting extracellular matrix to address chemoresistance

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A B S T R A C T

The tumor physical microenvironment (TPME) contributes to cancer chemoresistance in both mechanical and mechanobiological approaches. Along with chemotherapy, the tumor microenvironment undergoes dramatic changes, most of which can regulate TPME through extracellular matrix (ECM) remodeling and related signaling pathways. However, there is still no discussion about the post-chemotherapy TPME changes mediated by ECM remodeling, and consequent impact on chemoresistance. Herein, we summarize the TPME alterations induced by chemotherapy and corresponding influence on chemotherapy response of cancer cells in context of ECM. The response of cancer cell to chemotherapy, imposed by post-chemotherapy ECM, are discussed in both mechanical (ECM physical features) and mechanobiological (ECM-responsive signaling pathways) manner. In the end, we present ECM remodeling and related signaling pathways as two promising clinic strategies to relieve or overcome chemoresistance induced by TPME change, and summarize the corresponding therapeutic agents currently being tested in clinical trials.

1. Introduction

Despite constant advances in science and technology, the efficacy of chemotherapy is consistently challenged by the remarkable resilience of cancer cells. One of the critical challenges is the chemoresistance, which severely limits the efficacy of chemotherapy. Thus, a comprehensive understanding of chemoresistance is essential to ultimately defeat cancer.

In tissue, cells constantly communicate with their physical microenvironment (PME), and develop a responsive machinery for timely biological modulation. Tumor tissue is well-known for abnormal PME characteristics, including stiffness, microarchitecture, solid stress and interstitial fluid pressure (IFP) [1]. This aberrant tumor physical microenvironment (TPME) contributes to chemoresistance in two distinct ways: 1) in a mechanical manner—changed mechanical features put restriction on matter transfer [2]; and 2) in a mechanobiological manner—downstream biological signaling responding to mechanical changes [3,4]. Extracellular matrix (ECM) remodeling either directly regulate (stiffness and microarchitecture), or partially contribute to (solid stress and IFP) the aberrant TPME. Hence, ECM remodeling is recognized as the essential player in TPME-mediated chemoresistance and a potential target to alleviate chemoresistance. However, current studies typically fails to consider the dynamic change of TPME along with chemotherapy in exploration of TPME-mediated chemoresistance.

Recently, the post-chemotherapy TPME attract attention in the study of chemoresistance. Along with chemotherapy, dramatic changes occur in cancer tissues, including secretion of biochemical molecules (cytokines, chemokines, ECM proteins and proteases etc.) [5], alteration of reactive oxygen species (ROS) levels [6], activation of immune cell [7], transformation of cancer associated fibroblasts (CAFs) [7] and so on. Intriguingly, most of these changes closely relate with TPME regulation through ECM and related signaling pathways that further impacts cellular response to chemotherapy. Although there are several good reviews on the therapeutic potential of ECM in cancer treatment [8,9], until recently a review was published discussing the potential effect of post-chemotherapy ECM on chemotherapy responsiveness [10]. In the review, only the ECM-cell interaction is highlighted in discussion. Hence, there is still no comprehensive discussion about post-chemotherapy TPME change mediated by ECM remodeling, as well as its potential impact on chemoresistance.

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https://doi.org/10.1016/j.canlet.2023.216583
Received 22 September 2023; Received in revised form 28 November 2023; Accepted 30 November 2023
Available online 8 December 2023

Herein, we conclude that the TPME alterations induced by chemotherapy and corresponding influence on chemotherapy responsiveness (Fig. 1). These changes in response to chemotherapy induced by the post-chemotherapy ECM are discussed in both mechanical and mechanobiological manner (Fig. 1). In the end, we present ECM remodeling and ECM related biological pathways as two promising targets to relieve or overcome chemoresistance induced by TPME change, and summarize the corresponding therapeutic agents currently being tested in clinical trials.

2. Chemotherapy induced alteration in TPME

Post-chemotherapy TPME alterations, mediated by ECM, include direct modifications of component proteins and remodeling enzymes, and indirect regulation by cytokines and chemokines responsible for ECM remodeling. Besides, chemotherapy also alters ECM related pathways through the introduction of intracellular damage. Herein, the ECM related pathways are limited to the active sensing and responses of the cell to the ECM, although the ECM itself also participates in regulating pathways.

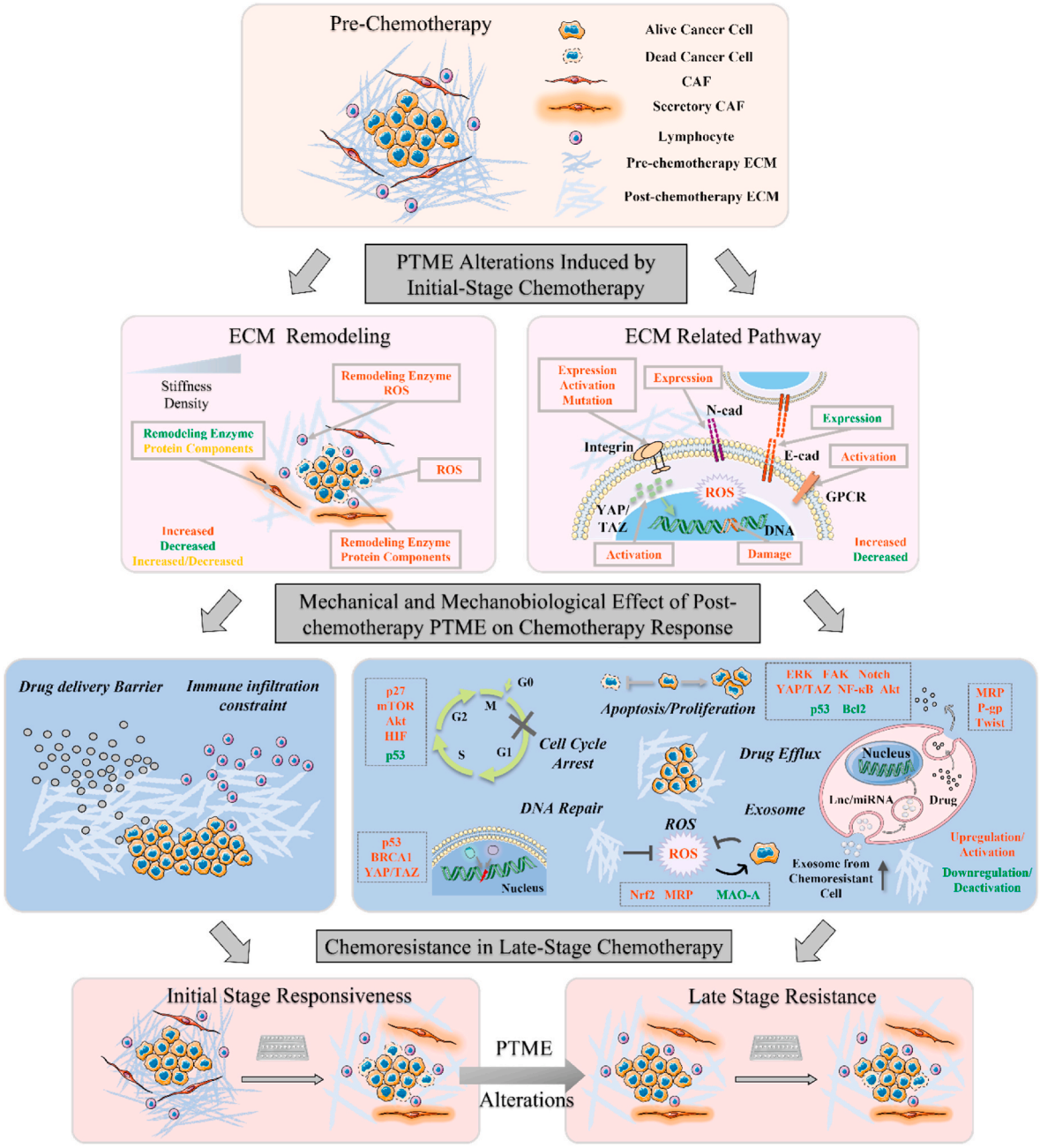

Fig. 1. The post-chemotherapy PTME alteration is mediated by ECM and consequentially mechanical and mechanobiological contribution to chemoresistance. The initial PTME (Top panel) undergoes alteration of ECM and related signaling pathways (Upper middle panel). After chemotherapy, the PTME appears to be altered in ECM and ECM related pathways and biological processes. The post-chemotherapy PTME contributes to the responses of cancer cells to late-stage chemotherapy in both mechanical and mechanobiological manner (Lower middle panel). These mechanical and mechanobiological factors of post-chemotherapy PTME work together to confer chemoresistance of cancer cells in late-stage chemotherapy (Bottom panel).

2.1. Chemotherapy induced TPME alteration is regulated by ECM remodeling

The post-chemotherapy change of ECM component is being elucidated by several recent studies (**Table 1**). For example, ECM undergoes progressively change along with platinum-based chemotherapy, which enhance chemoresistance of ovarian cancer cells [11]. In comparison of transcriptomic, histologic and clinical data of samples before and after chemotherapy, this chemotherapy-induced change in ECM particularly results from expression of ECM core proteins and affiliated proteins. Interestingly, upregulation of collagen VI is observed in solid tumors following chemotherapy, although the fragmented ECM is noticed simultaneously without clear explanation in the study [11]. Similarly, the upregulation of the other two collagen subtypes V and IV is reported after chemotherapy in liver cancer [12] and breast cancer [13], respectively. Quantitative proteomics has confirmed that chemotherapy induces drug-specific upregulation of collagen [12]. Moreover, chemotherapy can elevate deposition of hyaluronic acid (HA) and sulfated glycosaminoglycans (sGAGs) appears in glioblastoma [14]. The escalation expression and deposition of ECM proteins generally appear in cancer tissue along with chemotherapy.

ECM remodeling enzymes, metalloproteinase (MMP) and Lysyl oxidase (LOX), both show increased secretion after chemotherapy, although they play an opposite role in ECM remodeling. For example, the cancer cells secrete more MMP14 after chemotherapy in breast cancer [17] and melanoma [4]. In contrast, the post-chemotherapy expression of LOX is upregulated in breast cancer [16] and ovarian cancer [18]. Recent findings have demonstrated that chemotherapy promotes the secretion of LOX by immune cells [20]. Apart from the differences between cancer types, the paradoxical change of ECM remodeling enzymes possibly comes from both the different stages of tumor and treatment time with chemotherapeutics. According to a recent study [21], we suspect that cancer cells secrete more LOX to create a dense ECM for self-protection by limiting the transport of chemotherapeutics in the early stage of treatment; however, once they get used to chemotherapeutics in the late stage of treatment, they start to produce more MMP to degrade ECM for metastatic growth. Hence, the upregulation of both ECM enzymes contributes to the chemoresistance of cancer cells.

The main regulator of ECM production and remodeling, cancer associated fibroblasts (CAFs) are also influenced by chemotherapy. A recent single cell RNA-seq study shows that the preoperative chemotherapy (*e.g.*, oxaliplatin, leucovorin, 5-fluorouracil) can reduce ECM-remodeling CAFs, and induce the generation of myofibroblasts and several secretory CAFs in colorectal cancer [7]. Similarly, another study in pancreatic cancer patient show that chemotherapy switch the sub-TME into "deserted" status, which is ECM-rich, poorly-vascularized and CAF-depleted, and protects cancer cells from chemotherapy [21]. In contrast, the suppressive role of neoadjuvant chemotherapy (gemcitabine, paclitaxel, FOLFIRINOX regimen etc.), is reported on regulation of collagen (type I, III, IV, and V) expression by reducing the expression of ephrin-A5 in CAFs in pancreatic cancer [22]. In summary, the mechanism by which a specific chemotherapeutical agent leads to the CAF-mediated ECM changes remains elusive.

Recently, researchers have been paying attention to the role of cancer cells in post-chemotherapy ECM changes. For example, a variety of chemotherapies, including paclitaxel, doxorubicin, 5-fluorouracil and methotrexate, have been shown to activate the c-Jun N-terminal kinase (JNK) signaling pathway in breast cancer cells, which upregulates ECM proteins like secreted phosphoprotein 1 and tenascin C [23]. In addition, long-term gemcitabine treatment is shown to enhance the TGFβ-associated signals in pancreatic cancer cells, which alters the composition of the cancer stroma [24]. Consistently, enhanced TGFβ expression and secretion by ovarian and cervical cancer cells are induced by chemotherapy including doxorubicin, paclitaxel, cisplatin, and camptothecine [25].

Following chemotherapy, the increased reactive oxygen species (ROS) levels disrupt the redox homeostasis of cancer cells and tissues. Inside cell, the chemotherapy promotes ROS generation and accumulation in the mitochondria via disruption of electron transport system (ETS) and inhibition of cellular antioxidant system [6]. Cell death induced by chemotherapy triggers a proinflammatory response and the recruitment of leukocytes, which are responsible for extracellular ROS production [26]. Due to its influence on the production, assembly and turnover of the ECM, increased ROS levels drives excess ECM production in cancer tissues [26]. ROS can mediate the cross-linking reactions between tyrosine residues of ECM proteins, resulting in the increase of ECM stiffness [15]. In addition, tumor-secreted ROS promotes the differentiation of fibroblasts to myofibroblasts, which remodels the ECM in a highly active manner [19]. Collectively, chemotherapy-induced elevation of ROS profoundly regulates ECM stiffness and remodeling.

2.2. Chemotherapy induced TPME alteration is mediated by ECM regulated pathway

Chemotherapy also impacts ECM-cell interactions, by which cells sense and response to extracellular surroundings. Following chemotherapy, both expression and activity of cellular receptors interacting with the ECM appear changed. For example, in lung cancer, cisplatin induces the upregulation of α4, αv, β1, and β5 integrin, which enhances cell motility [27]. Moreover, in ovarian cancer [11] and melanoma [4], the activation of integrin is upregulated after chemotherapy. In urothelial cancer, chemotherapy drives mutations involving enhanced integrin expression and activation that promotes cancer cell survival, proliferation and metastasis, as evidenced by whole-exome sequencing and clonality analysis of patient samples [28]. Similarly, in a recent study, another ECM-cell interacting protein, N-cadherin, is approved to be upregulated in N-cadherin-enriched bladder cancer tissue subsets after neoadjuvant chemotherapy [29]. In line with N-cadherin upregulation, the post-chemotherapy downregulation of E-cadherin is reported in pancreatic cancer [30] and glioblastoma [14]. These results imply that chemotherapy can trigger EMT of cancer cells, which in turn helps cancer cells resist chemotherapy as EMT is recognized as one key contributor of chemoresistance [30,31].

Chemotherapy also indirectly affects ECM-cell interaction. One approach is the induction of DNA damage. The increased MMP-dependent invasiveness of cancer cells, for example, is associated with DNA damage [32] through the enhanced expression and activation of the transcription factor snail, which confers cancer cells with stem cell-like traits, and promotes chemoresistance, tumor recurrence and metastasis [33]. Although the exact mechanism is unclear, DNA damage can trigger cellular senescence [34], which endows cells the capability

Table 1
Summary of ECM protein change after chemotherapy.

ECM Protein	Cancer Types	Post-chemotherapy Change
Collagen I	Pancreatic cancer	Downregulation [15]
Collagen III	Pancreatic cancer	Downregulation [15]
Collagen IV	Breast cancer	Upregulation [16]
Collagen V	Liver cancer	Upregulation [17]
	Pancreatic cancer	Downregulation [15]
Collagen VI	Pancreatic cancer	Downregulation [15]
	Ovarian cancer	Upregulation [14]
Hyaluronic Acid	Glioblastoma	Upregulation [18]
Secreted phosphoprotein 1 (Osteopontin)	Breast cancer	Upregulation [19]
Sulfated Glycosaminoglycans	Glioblastoma	Upregulation [18]
Tenascin C	Breast cancer	Upregulation [19]

of remodeling ECM, including ECM deposition, cross-linking, and degradation [35]. Interestingly, the altered ECM and ECM-cell interaction in turn regulate cellular senescence. For example, integrin-mediated cell adhesion regulates cellular senescence through the βPAK-interacting exchange factor (βPIX)-G protein-coupled receptor kinase interacting protein (GIT) complex in senescent cells [36]. Another approach is the elevation of intracellular ROS level. It has been shown to that intracellular ROS levels can regulate cell-ECM adhesion and related signaling pathway by interfering phosphatase activity. For example, intracellular ROS promote the formation of focal adhesion by maintaining FAK hyperactivation in fibroblasts [37]. In glioma cells, ROS enhance expression and activation of integrin by the mediation of NADPH-oxidase and 5-lipoxygenase [38], both of which impact cellular response to chemotherapeutics. In summary, chemotherapy also indirectly influences the ECM-cell interaction through relevant signaling pathways activated by chemotherapy.

3. Chemotherapy resistance regulated by post-chemotherapy alteration of TPME

Mechanisms of chemoresistance development include poor drug delivery [2], activation of signaling pathways to escape cell death [39–41], increased DNA damage repair [42], and escalation of drug efflux or alteration of drug metabolism [43]. Considering the regulatory role of ECM-dependent TPME alteration in these processes, the post-chemotherapy changes of ECM and related pathways are believed to regulate response of cancer cells to chemotherapy in mechanical and mechanobiological manner, respectively.

3.1. Mechanical regulation of chemoresistance by post-chemotherapy TPME

One signature of post-chemotherapy TPME is the increased stiffness and density of the ECM, resulting from the accumulation of ECM components. Consequently, the intratissue mass transport switch from fast convection mode to slow diffusion mode [2], while cell migration are impeded due to the restricted space for movement [44]. These factors are thought to mechanically regulate the response to chemotherapy as they operate independently of mechanotransduction or biological pathways.

Drug delivery Barrier. The accumulation of ECM proteins increases the internal pressure of the cancer tissue and hence compresses the intratumoral blood vessels. The constriction of blood vessels restricts the transport of cancer drug, leading to the chemotherapy failure [2]. Cancers characterized with dense ECM, like pancreatic cancer [45] and sarcoma [46], are shown to be more resistant to chemotherapy. In addition, the dense ECM impedes the percolation and escape of interstitial fluid and unevenly elevates IFP [2]. As result, the transport mode of the drug switches from convection to diffusion, which is considerably slower for chemotherapeutic particles and molecules [2]. The impaired perfusion of drug, for example, is observed in colorectal cancer with ECM stiffening induced by anti-VEGF therapy [47]. Therefore, the physical constrains of the ECM thus limit the access of the drug to the cancer cells and impair the treatment outcome.

Immune infiltration constraint. One “side effect” of chemotherapy is its stimulatory impact on the activation and infiltration of immune cells, while an increase in cytokine production, known as "cytokine storm," upon chemotherapy, exhibits a similar effect [48]. Consistent with drug delivery, the high density of post-chemotherapy ECM potentially becomes physical barrier to immune cell infiltration [44]. In a mouse model of colorectal cancer, for example, a short-term treatment with oxaliplatin increases the infiltration of T-cells, which is suppressed along with the treatment [49]. In addition, after treatment of paclitaxel, the increased T-cell infiltration is observed in the first five days, but disappears two weeks later [50]. Considering the key challenge of T-cell infiltration, the physical constraints imposed by post-chemotherapy ECM are expected to cause this reversion, although these studies do not explore their interaction in detail.

3.2. Mechanobiological regulation of chemoresistance by post-chemotherapy TPME

The primary impact of post-chemotherapy PTME on chemoresistance arises from the ECM-mediated signaling pathways and biological activities. In response to the mechanical alterations of the ECM, cancer cells adjust their biological pathways and activities, including cell apoptosis and proliferation, cell cycle regulation, and DNA damage repair. These biological responses have been shown to concurrently influence the response of cancer cells to chemotherapy.

Apoptosis and Proliferation. Modulation of apoptosis and cell proliferation is the main mechanism by which cancer cells escape from chemotherapy. First, upregulation of the ECM protein itself can inhibit cell apoptosis. In ovarian cancer, for example, the upregulated collagen XI can activate TWIST1, which relieves chemotherapy damage by NF-κB mediated inhibition of apoptosis [39]. Consistently, the fibronectin-rich ECM protects cancer cells from chemotherapy by increased ERK1/2-mediated proliferation [51] or PI3K/Akt2-regulated inhibition of apoptosis [52], regardless of the post-chemotherapy excess secretion of fibronectin by the cells themselves [53], or of collagen and other ECM proteins by the surrounding cancer associated fibroblasts (CAFs) [54]. Similar regulation has also been reported for ECM proteins including versican [55] and lumican [56]. Upregulation of ECM remodeling enzyme, MMP, also promotes cell survival and proliferation via elevated activation of downstream pathways, including Notch [57] and integrin/FAK [4]. Similarly, inhibiting LOX induces apoptosis by reducing expression of ITGA5/FN1 to suppress FAK/Src signaling [16]. Along with increased ECM stiffness, enhanced activation of YAP/TAZ not only promotes cell survival to resist chemotherapy, but also shields mutation activating genes, including BRAF, KRAS and NRAS, from corresponding inhibitors, thereby promoting chemoresistance [58].

Meanwhile, the escalated expression and activity of cellular membrane protein responsible for ECM-cell communication, also regulates anti-apoptotic and pro-survival signaling pathways. For example, integrin can inhibit cancer cell apoptosis through FAK-PI3K-Akt/PKB signaling axis by direct upregulation of Bcl2 [59] or transcriptional regulation through NF-κB activation [60] or p53 inactivation [61]. Moreover, the high stiffness of post-chemotherapy ECM upregulates integrin [62], thereby further strengthening the related pathways. Currently, there is a lack of study evaluating the post-chemotherapy alteration of piezo, another classical ECM-cell communicator. However, upregulated expression and activation of piezo has been reported as result of ECM stiffening following chemotherapy [63]. In addition, 67LR, a laminin receptor, is upregulated after chemotherapy, which suppress apoptosis by Bcl2 [41], and promote cell growth by activation of protein phosphatase 2A (PP2A) [64].

DNA Repair. DNA damage is commonly observed in cancer cells following chemotherapy. The stiff ECM can shield the DNA from chemotherapeutic agents. When cells are cultured on soft ECM, accumulation of double-strand DNA damage (DSB) is observed due to inactivation of the ubiquitin pathway, which is required for recruiting DSB repair factors including BRCA1 and 53BP1 [65]. The ECM-mediated autophagy protects cancer cell from DNA damage through upregulation of DRAM-1, a activator of autophagy regulated by p53 in face of DNA damage [66]. Increased solid stress from deposition of ECM proteins can trigger dormancy of cancer cells and alter the DNA repair mode. In dormant liver cancer cells, for example, the error-prone non-homologous end joining (NHEJ) DNA repair is dominant, which leads to the generation and accumulation of DNA mutations [67]. ECM-regulated transcription, a constituent of cell mechano-transduction, also affects post-chemotherapy DNA repair. The iconic factor YAP/TAZ, for example, display the increased activation in response to stiff ECM, contributing to chemoresistance of cancer cells by

mitigating DNA damage in lung cancer [68] and liver cancer [69]. Together, these findings imply the chemotherapy-induced ECM alteration can enhance DNA damage repair, leading to chemoresistance of survival cells following chemotherapy.

Drug efflux. One key determinant of the responsiveness of cancer cells to chemotherapy is their ability to expel therapeutic molecules. Although the exact mechanism remains elusive, autophagy mediated by ECM-stiffening can increase drug efflux through upregulation of multidrug-resistance associated protein 1 (MRP1) in lung fibroblasts and P-glycoprotein (P-gp) in breast cancer [70], both of which are encoded by multidrug resistance (MDR) genes. Coincidently, the expression of MDR genes is also promoted by activation of HIF related pathways, resulting from shortage of oxygen in cancer tissues due to the excessive ECM deposition in various types of cancer [71]. Given that overexpression of Twist increases the expression of P-gp in colorectal cancer [72], the promotion of EMT by post-chemotherapy ECM alteration is highly capable to elevate the drug efflux of post-treatment cancer cells. In summary, the post-chemotherapy alteration of ECM promotes the drug efflux of cancer cells, thereby strengthening chemoresistance.

Cell Cycle Arrest. Cell cycle arrest, i.e., the non-cycling dormant status of cell, commonly appears after chemotherapy and is closely related to the cellular response to chemotherapy. It has been shown that ECM induces cell cycle arrest. In confined TPME, for example, the breast cancer cell cultured on a slow-relaxing (low viscous) gel becomes non-proliferative comparing with counterpart on a fast-relaxing (high viscous) gel, resulting from nuclear localization of the cell cycle inhibitor p27 (Kip1) [73]. On the fast-relaxing gel, TRPV4 channel is activated and consequently enhances the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which promotes the nuclear localization of Kip1. In addition, the escalated expression of laminin induce "dormancy" status of hepatic cancer cells through phosphorylation of mammalian target of rapamycin (mTOR), which helps them resist chemotherapeutic agents [74]. Moreover, hypoxia resulting from over-deposition of ECM protein also arrests the cell cycle of cancer cells via suppression of p53, helping them evade attack by chemotherapeutic agents that specifically target rapidly proliferating cells [75]. Although the exact mechanism is not clear, ECM remodeling is shown to play a role in "awakening" the dormant cancer cells. ECM remodeling mediated by neutrophil extracellular traps (NET), for example, can reactivate the proliferation of dormant cancer cells by NET-associated proteases, neutrophil elastase and MMP [76]. Together, the effect of chemotherapy-induced ECM remodeling on the regulation of cancer cell dormancy remains to be investigated.

ROS. The post-chemotherapy increase in ROS levels increases the expression and crosslinking of ECM proteins [26].This more compact ECM structure leads to the post-chemotherapy hypoxia in cancer tissue [77], and hence reversely increases extracellular ROS levels since oxidative phosphorylation becomes dysregulated in hypoxic cancer tissue. The effects of ROS on chemoresistance vary depending on the quantity present in the ECM. In the beginning of treatment, ROS level increases but still below the cytotoxic threshold, which helps cancer cells to adapt to the limited oxidative damage instead of causing cell death. For example, the nuclear factor erythroid 2-related factor 2 (Nrf2) upregulates anti-oxidant proteins and MRP1 in response to moderate increase in ROS levels induced by methotrexate-based chemotherapy [40]. These reactions contribute to chemoresistance by enhancing ROS neutralization and expulsion of ROS-inducing chemotherapeutics. When the continuously increasing expression of ECM proteins and their crosslinking elevate ROS levels beyond the cytotoxic threshold, this results in ROS-induced cell death. On the other hand, the increased ROS content also initiates angiogenesis in cancer tissue, which helps cells resist chemotherapy by constraining drug transportation and regulation of related signaling pathways [78]. In addition, ECM proteins are essential for intracellular ROS homeostasis. In a mice study, for example, the loss of collagen IV has been proven to escalate production of ROS in mitochondria via monoamine oxidase A (MAO-A) [79]. A similar effect is also reported in the patient with loss of the ECM fiber protein laminin221 [80]. In summary, a feedback loop between ECM and ROS level is initiated after chemotherapy, and ECM-mediated ROS levels affect cancer chemoresistance in a dose-dependent manner.

Exosome. Serve as a vital messenger for extracellular communication, exosomes secretion increases with increasing ECM stiffness for both stromal and cancer cells [81]. Recently, this exosome-mediated communication has been shown to promote chemoresistance. In breast cancer [82] and renal cancer [83], the exosomes from chemo-resistant cells effectively reduce the chemotherapeutic response of chemo-sensitive cells through gene regulation regulated by exosome-delivered RNAs, including micro RNAs (miRNA) [82] and long non-coding (lncRNAs) [83]. Exosomes derived from stromal cells, primarily fibroblasts, also contributes to the chemoresistance of cancer cells through the activation of survival signaling pathway (like Notch) [57] and priming cancer stem cells (CSCs) [84]. However, the question of whether the post-chemotherapy alteration of ECM promotes the secretion of chemo-resistant exosome by cancer cells that have survived from treatment requires further exploration.

4. Therapeutic strategies targeting post-chemotherapy TPME to address chemoresistance

Here, we discuss the therapeutic strategies potentially minimizing chemoresistance induced by post-chemotherapy TPME. The approach targeting ECM remodeling includes reduction of ECM protein deposition and ECM reorganization. For altered ECM related signaling, correction is the essential tactic. Here, we summarize the therapeutic agents targeting ECM remodeling and related signaling that are currently under clinical exploration (Fig. 2 and Table 2).

4.1. Mechanical therapies targeting post-chemotherapy TPME to address chemoresistance

ECM targeting strategies reduce or eliminate not only the whole mechanical contribution of the post-chemotherapy ECM on chemoresistance, but also the part of the mechanobiological contribution resulting from the altered ECM. To reduce post-chemotherapy ECM stiffening and densening, one strategy is to inhibit excessive ECM synthesis and crosslinking, and the other is to promote ECM degradation.

Due to its dominant role in promoting ECM production, TGF-β is a promising target to interfere with excessive ECM synthesis. Current attempts to inhibit TGF-β activity specifically focus on three aspects (well-reviewed in Ref. [85]): 1) reduction of TGF-β expression by siRNA-based or antisense oligonucleotide like AP12009, TRK250 and STP705; 2) blocking of binding to cellular receptors by neutralizing antibodies like SAR439459, NIS793 and ABBV151, as well as receptor inhibitors like TEW-7197, LY3200882 and GFH018; 3) inhibition of downstream signaling pathways by factor inhibitors like LY2157299 and PF-06952229 (Fig. 2 and Table 2). Most of the therapeutical approaches have so far shown good efficacy in preclinical studies. However, both the complexity of the cancer tissues and the systemic effect of TGF-β may results in the subtle efficacy in clinical trials. Recently, the new strategy is being evaluated in combination with other therapies to improve anti-cancer effect of TGF-β interference. Moreover, novel strategies to directly intervene ECM production are continuously being explored in preclinical studies. For example, a natural hormone relaxin is shown to effectively suppress ECM deposition by promoting the activity of ECM-degrading proteases in several preclinical fibrosis models [86]. The hyaluronic acid (HA) synthesis inhibitor 4-methylumbelliferone (4-MU) [87] and HA degrading enzyme PEGPH20 [88] both increase the therapeutic effect of chemotherapy, radiotherapy and immunotherapy. Endowing these drugs with new application scenarios helps the development of therapy targeting ECM alteration-induced chemoresistance after chemotherapy.

Both the ECM crosslinking and degradation contribute to its

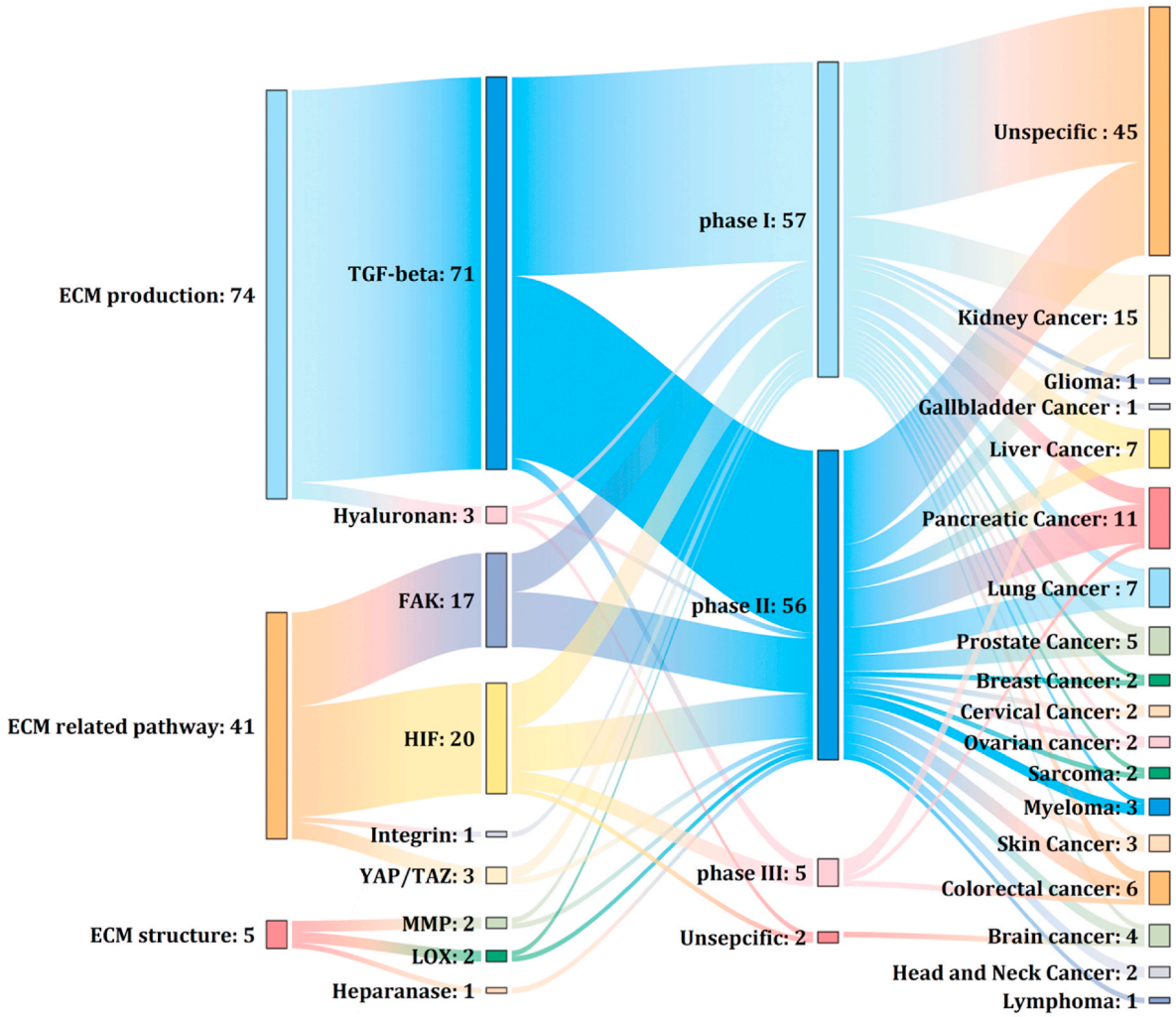

Fig. 2. The strategies targeting ECM and related pathways to address chemotherapy under clinical trials. The Sankey diagram summarizes the currently active clinical trials potentially addressing chemoresistance by targeting ECM remodeling (protein production and structure) and ECM related pathways. The category consists of corresponding proteins or biological molecules, which are further classified based on the ongoing phase of the trial and the type of cancer being studied in each trial. The unspecific means the relevant information is absent in the description of clinical trials.

remodeling, a process mainly regulated by two ECM proteases, MMPs and LOX. The post-chemotherapy upregulation of MMPs has been demonstrated in multiple cancers [89], although the mechanism remains unclear. MMP-targeting therapy, mainly small molecule inhibitors, currently undergo extensive exploration to treat cancer and eliminate chemoresistance [90]. However, there still exist challenges such as the effects of broad-spectrum inhibition and reduction of efficacy along with treatment. Recently, the development of neutralizing antibodies offer a promising alternative (Fig. 2 and Table 2). Notwithstanding that inhibitor β-aminopropionitrile (BAPN) is a widely-used research tool to reduce ECM stiffness, it fails in clinical trials due to high toxicity [91]. Other attempts are made to develop safer and more effective therapeutic approaches including neutralizing antibody Simtuzumab [92] and small molecule inhibitors PXS-5005 [93].

4.2. Mechanobiological therapies targeting post-chemotherapy TPME to address chemoresistance

Chemotherapy also alters ECM-cell crosstalk, which is an essential step in the mechanobiological response of the cells. The abnormal alteration of ECM-related pathways typically enhances cell resistance to chemotherapy through regulation of cell proliferation, apoptosis and dormancy, etc. The participants of pathway regulation can be simply catalogized into cytoplasmic (integrin, FAK and piezo etc.) and nucleoplasmic (YAP/TAZ, Twist and NF-κB, etc.) ones, according to their intracellular localization.

As an ionic cytoplasmic player, integrin is the prior target to interfere with ECM-cell crosstalk. Many approaches have been developed to target integrins [94], ranging from genetic interference to binding blocking antibodies and small molecule inhibitors. Unfortunately, none of these approaches have been ultimately used in cancer treatment, although several are successful in pre-clinical and phase I/II trails. For example, the clinical trial of integrin αvβ3/αvβ5 neutralizing antibody (EMD 121974) is terminated in phase II without apparent efficacy [95]. Currently one integrinβ1 targeting antibody is being tested in a clinical trial with the good preclinical result (**Table 2**). Inhibition of FAK, downstream signaling of integrin, has emerged as an alternative of integrin targeting therapy [96]. Beside integrin signaling, FAK also regulates receptor tyrosine kinase signaling, which makes FAK inhibition more attractive in development of cancer treatment (Fig. 2 and Table 2). The combination therapy of FAK inhibition with other clinical cancer treatments (chemotherapy and immunotherapy) gained lots of interest in clinical trials with promising preclinical result [96]. Interestingly, in combination with chemotherapy, radiotherapy and targeted

Table 2
The summary of current clinical trials targeting ECM and related pathways.

Target	Therapeutic Approach	Name	Cancer Types	Trial ID (Phase)
TGF-beta	Monoclonal Ab	Fresolimumab	Lung Cancer	NCT02581787 (I/II)
		SAR-439459	Liver Cancer	NCT04524871 (I/II)
			Myeloma	NCT04643002 (I/II)
			Unspecific	NCT04729725 (I)
		NIS793	Pancreatic Cancer	NCT04935359 (III), NCT04390763 (II)
		ABBV151	Unspecific	NCT03821935 (I)
	Bifunctional fusion protein	Bintrafusp Alfa	Breast Cancer	NCT03620201 (I)
			Cervical Cancer	NCT04432597 (I/II)
			Colorectal cancer	NCT03436563 (I/II), NCT04708470 (I/II)
			Gallbladder Cancer	NCT04349280 (I)
			Head and Neck Cancer	NCT04595149 (II)
			Lung Cancer	NCT03554473 (I/II), NCT05005429 (II), NCT04396535 (II)
			Lymphoma	NCT04417660 (II)
			Prostate Cancer	NCT04633252 (I/II), NCT03493945 (I/II)
			Sarcoma	NCT04303117 (I/II)
			Unspecific	NCT04235777 (I), NCT04574583 (I/II), NCT04287868 (I/II), NCT04789668 (I/II)
		SHR-1701	Colorectal cancer	NCT04856787 (II/III)
			Unspecific	NCT03710265 (I), NCT03774979 (I), NCT04856774 (I/II), NCT04407741 (I/II)
		TST005	Unspecific	NCT04958434 (I)
		QLS31901	Unspecific	NCT04954456 (I)
	Monoclonal Ab & Bifunctional fusion protein	JS201	Unspecific	NCT04956926 (I)
	Small molecule	GFH018	Unspecific	NCT04914286 (I/II)
		LY2157299 (Galunisertib)	Head and Neck Cancer	NCT04605562 (II)
	Antisense oligonucleotide against TGF-β	STP705	Liver Cancer	NCT04676633 (I)
			Skin Cancer	NCT04669808 (II), NCT04844983 (II)
		TASO-001	Unspecific	NCT04862767 (I)
	TGF-β receptor inhibitor	TEW-7197 (Vactosertib)	Pancreatic Cancer	NCT03666832 (I/II)
		LY3200882	Unspecific	NCT02937272 (I)
		GT90001	Liver Cancer	NCT03893695 (I/II)
			Unspecific	NCT04984668 (I/II)
Hyaluronan	Peptides	PEGPH20	Pancreatic Cancer	NCT01959139 (I/II), NCT02921022 (U)
Metalloproteinase	Bifunctional fusion protein	BT1718	Unspecific	NCT03486730 (I/II)
Lysyl oxidase	Small molecule	PXS-5505	Liver Cancer	NCT04676529 (I/II)
Heparanase	Small molecule	PG545	Unspecific	NCT05061017 (II)
Integrin	Monoclonal Ab	OS2966	Glioma	NCT04608812 (I)
Focal adhesion kinase (FAK)	Small molecule	Defactinib	Brain Cancer	NCT05798507(I)
			Lung Cancer	NCT04620330 (II)
			Myeloma	NCT04439331 (II)
			Ovarian cancer	NCT03287271 (I/II)
			Pancreatic cancer	NCT04331041 (II), NCT03727880 (II)
			Unspecific	NCT03875820 (I), NCT02758587 (I/II), NCT05512208 (II)
		APG-2449	Unspecific	NCT03917043 (I)
		AMP945	Pancreatic cancer	NCT05355298 (I/II)
		IN10018	Melanoma	NCT04109456 (I)
		GSK2256098	Pancreatic cancer	NCT02428270 (II)
			Brain cancer	NCT02523014 (II)
YAP/TAZ	Small molecule	IAG933	Unspecific	NCT04857372 (I)
		Zoledronate	Breast Cancer	NCT03358017(II)
		IK-930	Unspecific	NCT05228015 (I)
Hypoxia Inducable Factor (HIF)	Small molecule	Belzutifan	Kidney Cancer	NCT04627064(I), NCT04846920(I), NCT05030506(I), NCT03634540(II), NCT05468697(I/II), NCT04489771(II), NCT04195750(III), NCT04736706 (III), NCT05239728(III)
			Unspecific	NCT02974738 (I), NCT04924075(II)
		Propranolol	Brain cancer	NCT05424016 (U)
		DFF332	Kidney Cancer	NCT04895748 (I)
		NKT2152	Kidney Cancer	NCT05119335(I/II)
		MBM-02	Brain cancer	NCT04874506(II)
			Prostate Cancer	NCT04876755(II)

therapy, the FAK inhibition appears to reverse the adaptive resistance of cancer cells to these therapies [96], which highlights its potential as an ideal target to relieve chemoresistance induced by post-chemotherapy ECM.

The nucleoplasmic player mainly composed of transcription factors (TFs) and associated proteins, the actual regulator of gene expression in response to ECM changes. Among them, YAP is the particularly intriguing one due to its extensive involvement in many mechanisms of chemoresistance [11,58,69]. As a mechano-sensor responding to diverse physical stimuli, YAP has been demonstrated to be controlled by multiple ECM proteins including collagen [11], fibronectin [97] and argin [98]. Meanwhile, YAP can reversely regulate the expression of ECM proteins [97], implying a potential regulatory feedback loop between YAP and ECM proteins. Considering the profound regulation of YAP in the transcription of diverse genes, it is important to determine the contribution of drug-targeted YAP to YAP-regulated response to chemotherapy. For example, YAP can regulate both cell survival and apoptosis, so which one should be selected as a target? There are several undergoing clinical trials to estimate the potential of YAP as a novel target of cancer treatment (Fig. 2 and Table 2). However, the efficiency of targeting YAP still requires further evaluation in the context of ECM mediated signaling altered by chemotherapy. Efforts are made to interfere with other TFs as well. For example, multiple approaches are developed to inhibit NF-κB activity, including interference of binding with DNA, interaction with other transcription cofactors and miRNA knockdown of NF-κB activator protein [99]. Nevertheless, no major progress has been made in cancer treatment based on these approaches, although corresponding clinical trials have been completed.

5. Conclusions and future perspectives

Chemoresistance is a key challenge in cancer treatment. Recently, chemotherapy has been reported to induce PTME alteration via ECM remodeling and related pathways, which are implied to further impact chemoresistance. The ECM-mediated PTME change can contribute to chemoresistance in both mechanical and mechanobiological manner. These two different aspects are often discussed separately in the majority of current studies, although they collaborate to regulate chemoresistance. This interaction appears increasingly crucial in circumstances of post-chemotherapy resistance as discussed in this review. Thus, both the mechanical and mechanobiological contributions of ECM should be considered to understand the role of PTME on chemotherapy responsiveness and select converging targets for treatment.

Moreover, the impact of chemotherapy on PTME highly depends on the cellular composition and biochemical factors within the cancer tissue. The diverse and even contradictory effect of specific chemotherapeutical agents on ECM remodeling raises a fundamental question: how can we identify the optimal strategy for individual case? In our opinion, the complete understanding of the fundamental mechanism for chemotherapy induced change of ECM remodeling and related pathways is of utmost value. The development of *in-vivo* and *in-vitro* PTME model reproducing the dynamic interaction between cancer cells, stromal cells and ECM, also helps us understand the alteration of ECM-related pathways induced by chemotherapy.

Currently, therapy targeting ECM gives interesting and promising outcomes, implying great potential as an adjuvant for chemotherapy [9,97]. However, there are still several challenges to normalizing post-chemotherapy ECM by targeted therapies. Given the heterogeneity of cancer cell, can we select a correlative and robust biomarker as an ideal target? Will the complex mechanobiological interaction between cancer cells and ECM give off-target effects? In addition, the crosstalk between the immune system and ECM changes needs attention. Hopefully, the outcome-oriented backward inference may provide an alternative to screen effective targets for chemotherapeutics design. The drug currently employed in clinical practice to intervene in ECM protein production and crosslinking helps selection of druggable candidates for preliminary trials, thus assisting in the inference of the most valuable target. Moreover, it is of great help to construct a comprehensive database of PTME features along with chemotherapy. Undoubtedly, analyzing such extensive data is challenging, but AI can provide substantial assistance. A new concept “mechano-medicine” is emerging in the field, aiming to diagnose, understand and intervene in diseases from the perspective of biomechanics and mechanobiology. We believe that the strategy targeting ECM has great potential to become a vital part of mechanotherapy.

Expanding focus from naïve TPME to post-chemotherapy TPME helps people understand chemoresistance and cancer reoccurrence better. Although great work has been done to identify and analyze the change of TPME regulated by ECM, the global change of post-chemotherapy TPME remain inexplicable. The good characterization and quantification of overall TPME changes not only offer a comprehensive picture of the impact induced by chemotherapy on TPME, but also benefit the construction of *in-vitro* model for exploring post-chemotherapy TPME, which eventually facilitates the design of appropriate chemotherapeutic agents to defeat chemoresistance.

CRediT authorship contribution statement

Yuan Li: Writing – review & editing, Writing – original draft, Conceptualization. **Guorui Jin:** Writing – review & editing. **Na Liu:** Writing – review & editing. **Hui Guo:** Writing – review & editing. **Feng Xu:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was financially supported by the National Natural Science Foundation of China (12102334, 31971293, and 82072701), by the Open Funds for Shaanxi Provincial Key Laboratory of Infection and Immune Diseases (2022-MS-1), the National Key R&D Program of China (2021YFE0202400), CSCO-MSD Innovation Fund Key Projects (Y-MSD2020-0247).

References

[1] H.D.T. Nia, L.L. Munn, R.K. Jain, Physical traits of cancer, Science 370 (546) (2020) 541–549.
[2] C.H. Heldin, K. Rubin, K. Pietras, A. Ostman, High interstitial fluid pressure - an obstacle in cancer therapy, Nat. Rev. Cancer 4 (2004) 806–813.
[3] E. Hirata, M.R. Girotti, A. Viros, S. Hooper, B. Spencer-Dene, M. Matsuda, J. Larkin, R. Marais, E. Sahai, Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin beta 1/FAK signaling, Cancer Cell 27 (2015) 574–588.
[4] C. Marusak, V. Thakur, Y. Li, J.T. Freitas, P.M. Zmina, V.S. Thakur, M. Chang, M. Gao, J.F. Tan, M. Xiao, Y.L. Lu, G.B. Mills, K. Flaherty, D.T. Frederick, B. C. Miao, R.J. Sullivan, T. Moll, G.M. Boland, M. Herlyn, G. Zhang, B. Bedogni, Targeting extracellular matrix remodeling restores BRAF inhibitor sensitivity in BRAFi-resistant melanoma, Clin. Cancer Res. 26 (2020) 6039–6050.
[5] G. Karagiannis, J. Condeelis, M. Oktay, Chemotherapy-induced metastasis: molecular mechanisms, clinical manifestations, therapeutic interventions, Cancer Res. 79 (2019) 4567–4576.
[6] H. Yang, R.M. Villani, H. Wang, M.J. Simpson, M.S. Roberts, M. Tang, X. Liang, The role of cellular reactive oxygen species in cancer chemotherapy, J. Exp. Clin. Cancer Res. 37 (2018).
[7] L.-H. Che, J.-W. Liu, J.-P. Huo, R. Luo, R.-M. Xu, C. He, Y.-Q. Li, A.-J. Zhou, P. Huang, Y.-Y. Chen, W. Ni, Y.-X. Zhou, Y.-Y. Liu, H.-Y. Li, R. Zhou, H. Mo, J.-M. Li, A single-cell atlas of liver metastases of colorectal cancer reveals reprogramming of the tumor microenvironment in response to preoperative chemotherapy, Cell Discovery 7 (2021).
[8] E. Henke, R. Nandigama, S. Ergun, Extracellular matrix in the tumor microenvironment and its impact on cancer therapy, Front. Mol. Biosci. 6 (2020).

[9] J. Huang, L. Zhang, D. Wan, L. Zhou, S. Zheng, S. Lin, Y. Qiao, Extracellular matrix and its therapeutic potential for cancer treatment, Signal Transduct. Targeted Ther. 6 (2021).
[10] J. Gonzalez-Molina, L. Moyano-Galceran, A. Single, O. Gultekin, S. Alsalhi, K. Lehti, Chemotherapy as a regulator of extracellular matrix-cell communication: implications in therapy resistance, Semin. Cancer Biol. 86 (2022) 224–236.
[11] E.A. Pietilae, J. Gonzalez-Molina, L. Moyano-Galceran, S. Jamalzadeh, K. Zhang, L. Lehtinen, S.P. Turunen, T.A. Martins, O. Gultekin, T. Lamminen, K. Kaipio, U. Joneborg, J. Hynninen, S. Hietanen, S. Grenman, R. Lehtonen, S. Hautaniemi, O. Carpen, J.W. Carlson, K. Lehti, Co-evolution of matrisome and adaptive adhesion dynamics drives ovarian cancer chemoresistance, Nat. Commun. 12 (2021).
[12] J.R. Guarin, J.P. Fatherree, M.J. Oudin, Chemotherapy treatment induces pro-invasive changes in liver ECM composition, Matrix Biol. 112 (2022) 43–61.
[13] J.P. Fatherree, J.R. Guarin, R.A. McGinn, S.P. Naber, M.J. Oudin, Chemotherapy-induced collagen IV drives cancer cell motility through activation of src and focal adhesion kinase, Cancer Res. 82 (2022) 2031–2044.
[14] A. Chandra, A. Jahangiri, W.C. Chen, A.T. Nguyen, G. Yagnik, M.P. Pereira, S. Jain, J.H. Garcia, S.S. Shah, H. Wadhwa, R.S. Joshi, J. Weiss, K.J. Wolf, J.-M.G. Lin, S. Mueller, J.W. Rick, A.A. Diaz, L.A. Gilbert, S. Kumar, M.K. Aghi, Clonal ZEB1-driven mesenchymal transition promotes targetable oncologic antiangiogenic therapy resistance, Cancer Res. 80 (2020) 1498–1511.
[15] J.M. Larios, R. Budhiraja, B.L. Fanburg, V.J. Thannickal, Oxidative protein cross-linking reactions involving L-tyrosine in transforming growth factor-beta 1-stimulated fibroblasts, J. Biol. Chem. 276 (2001) 17437–17441.
[16] O. Saatci, A. Kaymak, U. Raza, P.G. Ersan, O. Akbulut, C.E. Banister, V. Sikirzhytski, U.M. Tokat, G. Aykut, S.A. Ansari, H.T. Dogan, M. Dogan, P. Jandaghi, A. Isik, F. Gundogdu, K. Kosemehmetoglu, O. Dizdar, S. Aksoy, A. Akyol, A. Uner, P.J. Buckhaults, Y. Riazalhosseini, O. Sahin, Targeting lysyl oxidase (LOX) overcomes chemotherapy resistance in triple negative breast cancer, Nat. Commun. 11 (2020).
[17] V. Thakur, K. Zhang, A. Savadelis, P. Zmina, B. Aguila, S.M. Welford, F. Abdul-Karim, K.W. Bonk, R.A. Keri, B. Bedogni, The membrane tethered matrix metalloproteinase MT1-MMP triggers an outside-in DNA damage response that impacts chemo- and radiotherapy responses of breast cancer, Cancer Lett. 443 (2019) 115–124.
[18] L. Ryner, Y. Guan, R. Firestein, Y. Xiao, Y. Choi, C. Rabe, S. Lu, E. Fuentes, L.-Y. Huw, M.R. Lackner, L. Fu, L.C. Amler, C. Bais, Y. Wang, Upregulation of periostin and reactive stroma is associated with primary chemoresistance and predicts clinical outcomes in epithelial ovarian cancer, Clin. Cancer Res. 21 (2015) 2941–2951.
[19] N. Sampson, R. Koziel, C. Zenzmaier, L. Bubendorf, E. Plas, P. Jansen-Duerr, P. Berger, ROS signaling by NOX4 drives fibroblast-to-myofibroblast differentiation in the diseased prostatic stroma, Mol. Endocrinol. 25 (2011) 503–515.
[20] J. Haj-Shomaly, A. Vorontsova, T. Barenholz-Cohen, O. Levi-Galibov, M. Devarasetty, M. Timaner, Z. Raviv, T.J. Cooper, S. Soker, P. Hasson, D. Weihs, R. Scherz-Shouval, Y. Shaked, T cells promote metastasis by regulating extracellular matrix remodeling following chemotherapy, Cancer Res. 82 (2022) 278–291.
[21] B.T. Grunwald, A. Devisme, G. Andrieux, F. Vyas, K. Aliar, C.W. McCloskey, A. Macklin, G.H. Jang, R. Denroche, J.M. Romero, P. Bavi, P. Bronsert, F. Notta, G. O'Kane, J. Wilson, J. Knox, L. Tamblyn, M. Udaskin, N. Radulovich, S.E. Fischer, M. Boerries, S. Gallinger, T. Kislinger, R. Khokha, Spatially confined sub-tumor microenvironments in pancreatic cancer, Cell 184 (2021) 5577–+.
[22] K. Nakajima, Y. Ino, C. Naito, S. Nara, M. Shimasaki, U. Ishimoto, T. Iwasaki, N. Doi, M. Esaki, Y. Kishi, K. Shimada, N. Hiraoka, Neoadjuvant therapy alters the collagen architecture of pancreatic cancer tissue via Ephrin-A5, Br. J. Cancer 126 (2022) 628–639.
[23] J. Insua-Rodriguez, M. Pein, T. Hongu, J. Meier, A. Descot, C.M. Lowy, E. De Braekeleer, H.-P. Sinn, S. Spaich, M. Suetterlin, A. Schneeweiss, T. Oskarsson, Stress signaling in breast cancer cells induces matrix components that promote chemoresistant metastasis, EMBO Mol. Med. 10 (2018).
[24] D.R. Principe, M. Narbutis, S. Kumar, A. Park, N. Viswakarma, M.J. Dorman, S. D. Kamath, P.J. Grippo, M.L. Fishel, R.F. Hwang, D. Thummuri, P.W. Underwood, H.G. Munshi, J.G. Trevino, A. Rana, Long-term gemcitabine treatment reshapes the pancreatic tumor microenvironment and sensitizes murine carcinoma to combination immunotherapy, Cancer Res. 80 (2020) 3101–3115.
[25] H. Zhu, X. Gu, L. Xia, Y. Zhou, H. Bouamar, J. Yang, X. Ding, C. Zwieb, J. Zhang, A. P. Hinck, L.-Z. Sun, X. Zhu, A novel TGF beta trap blocks chemotherapeutics-induced TGF beta 1 signaling and enhances their anticancer activity in gynecologic cancers, Clin. Cancer Res. 24 (2018) 2780–2793.
[26] J.A. Eble, F.F. de Rezende, Redox-relevant aspects of the extracellular matrix and its cellular contacts via integrins, Antioxidants Redox Signal. 20 (2014) 1977–1993.
[27] A. Maiuthed, P. Chanvorachote, Cisplatin at sub-toxic levels mediates integrin switch in lung cancer cells, Anticancer Res. 34 (2014) 7111–7117.
[28] B.M. Faltas, D. Prandi, S.T. Tagawa, A.M. Molina, D.M. Nanus, C. Sternberg, J. Rosenberg, J.M. Mosquera, B. Robinson, O. Elemento, A. Sboner, H. Beltran, F. Demichelis, M.A. Rubin, Clonal evolution of chemotherapy-resistant urothelial carcinoma, Nat. Genet. 48 (2016) 1490–1499.
[29] K.H. Gouin III, N. Ing, J.T. Plummer, C.J. Rosser, B. Ben Cheikh, C. Oh, S.S. Chen, K.S. Chan, H. Furuya, W.G. Tourtellotte, S.R.V. Knott, D. Theodorescu, An N-Cadherin 2 expressing epithelial cell subpopulation predicts response to surgery, chemotherapy and immunotherapy in bladder cancer, Nat. Commun. 12 (2021).
[30] C. Carbone, T. Moccia, C. Zhu, G. Paradiso, A. Budillon, P.J. Chiao, J. L. Abbruzzese, D. Melisi, Anti-VEGF treatment-resistant pancreatic cancers secrete proinflammatory factors that contribute to malignant progression by inducing an EMT cell phenotype, Clin. Cancer Res. 17 (2011) 5822–5832.
[31] M. Debaugnies, S. Rodriguez-Acebes, J. Blondeau, M.-A. Parent, M. Zocco, Y. Song, V. de Maertelaer, V. Moers, M. Latil, C. Dubois, K. Coulonval, F. Impens, D. Van Haver, S. Dufour, A. Uemura, P.A. Sotiropoulou, J. Mendez, C. Blanpain, RHOJ controls EMT-associated resistance to chemotherapy, Nature 616 (2023) 168–175.
[32] G.P.d.F. Nader, S. Aguera-Gonzalez, F. Routet, M. Gratia, M. Maurin, V. Cancila, C. Cadart, A. Palamidessi, R.N. Ramos, M. San Roman, M. Gentili, A. Yamada, A. Williart, C. Lodillinsky, E. Lagoutte, C. Villard, J.-L. Viovy, C. Tripodo, J. Galon, G. Scita, N. Manel, P. Chavrier, M. Piel, Compromised nuclear envelope integrity drives TREX1-dependent DNA damage and tumor cell invasion, Cell 184 (2021) 5230. -+.
[33] Y. Wang, J. Shi, K. Chai, X. Ying, B.P. Zhou, The role of snail in EMT and tumorigenesis, Curr. Cancer Drug Targets 13 (2013) 963–972.
[34] J. Guillon, C. Petit, B. Toutain, C. Guette, E. Lelievre, O. Coqueret, Chemotherapy-induced senescence, an adaptive mechanism driving resistance and tumor heterogeneity, Cell Cycle 18 (2019) 2385–2397.
[35] E. Mavrogonatou, H. Pratsinis, A. Papadopoulou, N.K. Karamanos, D. Kletsas, Extracellular matrix alterations in senescent cells and their significance in tissue homeostasis, Matrix Biol. 75–76 (2019) 27–42.
[36] E.-Y. Shin, J.-H. Park, S.-T. You, C.-S. Lee, S.-Y. Won, J.-J. Park, H.-B. Kim, J. Shim, N.-K. Soung, O.-J. Lee, M.A. Schwartz, E.-G. Kim, Integrin-mediated adhesions in regulation of cellular senescence, Sci. Adv. 6 (2020).
[37] P. Chiarugi, G. Pani, E. Giannoni, L. Taddei, R. Colavitti, G. Raugei, M. Symons, S. Borrello, T. Galeotti, G. Ramponi, Reactive oxygen species as essential mediators of cell adhesion: the oxidative inhibition of a FAK tyrosine phosphatase is required for cell adhesion, JCB (J. Cell Biol.) 161 (2003) 933–944.
[38] C.-S. Xu, Z.-F. Wang, X.-D. Huang, L.-M. Dai, C.-J. Cao, Z.-Q. Li, Involvement of ROS-alpha v beta 3 integrin-FAK/Pyk2 in the inhibitory effect of melatonin on U251 glioma cell migration and invasion under hypoxia, J. Transl. Med. 13 (2015).
[39] Y.-H. Wu, Y.-F. Huang, T.-H. Chang, C.-Y. Chou, Activation of TWIST1 by COL11A1 promotes chemoresistance and inhibits apoptosis in ovarian cancer cells by modulating NF-kappa B-mediated IKK beta expression, Int. J. Cancer 141 (2017) 2305–2317.
[40] Y. Shen, J. Yang, J. Zhao, C. Xiao, C. Xu, Y. Xiang, The switch from ER stress-induced apoptosis to autophagy via ROS-mediated JNK/p62 signals: a survival mechanism in methotrexate-resistant choriocarcinoma cells, Exp. Cell Res. 334 (2015) 207–218.
[41] C.-L. Lu, J. Xu, H.-J. Yao, K.-L. Luo, J.-M. Li, T. Wu, G.-Z. Wu, Inhibition of human 67-kDa laminin receptor sensitizes multidrug resistance colon cancer cell line SW480 for apoptosis induction, Tumor Biol. 37 (2016) 1319–1325.
[42] K.M. Sakthivel, S. Hariharan, Regulatory players of DNA damage repair mechanisms: role in Cancer Chemoresistance, Biomed. Pharmacother. 93 (2017) 1238–1245.
[43] M.M. Gottesman, T. Fojo, S.E. Bates, Multidrug resistance in cancer: role of ATP-dependent transporters, Nat. Rev. Cancer 2 (2002) 48–58.
[44] H. Guo, T. Zhang, Y. Yu, F. Xu, Cancer physical hallmarks as new targets for improved immunotherapy, Trends Cell Biol. 31 (2021) 520–524.
[45] S. Dangi-Garimella, S.B. Krantz, M.R. Barron, M.A. Shields, M.J. Heiferman, P. J. Grippo, D.J. Bentrem, H.G. Munshi, Three-Dimensional collagen I promotes gemcitabine resistance in pancreatic cancer through MT1-MMP-mediated expression of HMGA2, Cancer Res. 71 (2011) 1019–1028.
[46] L. Eikenes, O.S. Bruland, C. Brekken, C.D.L. Davies, Collagenase increases the transcapillary pressure gradient and improves the uptake and distribution of monoclonal antibodies in human osteosarcoma xenografts, Cancer Res. 64 (2004) 4768–4773.
[47] N.N. Rahbari, D. Kedrin, J. Incio, H. Liu, W.W. Ho, H.T. Nia, C.M. Edrich, K. Jung, J. Daubriac, I. Chen, T. Heishi, J.D. Martin, Y. Huang, N. Maimon, C. Reissfelder, J. Weitz, Y. Boucher, J.W. Clark, A.J. Grodzinsky, D.G. Duda, R.K. Jain, D. Fukumura, Anti-VEGF therapy induces ECM remodeling and mechanical barriers to therapy in colorectal cancer liver metastases, Sci. Transl. Med. 8 (2016), 360ra135.
[48] G.S. Karagiannis, J.M. Pastoriza, Y. Wang, A.S. Harney, D. Entenberg, J. Pignatelli, V.P. Sharma, E.A. Xue, E. Cheng, T.M. D'Alfonso, J.G. Jones, J. Anampa, T. E. Rohan, J.A. Sparano, J.S. Condeelis, M.H. Oktay, Neoadjuvant chemotherapy induces breast cancer metastasis through a TMEM-mediated mechanism, Sci. Transl. Med. 9 (2017).
[49] W. Wang, L. Wu, J. Zhang, H. Wu, E. Han, Q. Guo, Chemoimmunotherapy by combining oxaliplatin with immune checkpoint blockades reduced tumor burden in colorectal cancer animal model, Biochem. Biophys. Res. Commun. 487 (2017) 1–7.
[50] J. Peng, J. Hamanishi, N. Matsumura, K. Abiko, K. Murat, T. Baba, K. Yamaguchi, N. Horikawa, Y. Hosoe, S.K. Murphy, I. Konishi, M. Mandai, Chemotherapy induces programmed cell death-ligand 1 overexpression via the nuclear factor-kappa B to foster an immunosuppressive tumor microenvironment in ovarian cancer, Cancer Res. 75 (2015) 5034–5045.
[51] S.W. Han, N. Sidell, J. Roman, Fibronectin stimulates human lung carcinoma cell proliferation by suppressing p21 gene expression via signals involving Erk and Rho kinase, Cancer Lett. 219 (2005) 71–81.
[52] H. Xing, D. Weng, G. Chen, W. Tao, T. Zhu, X. Yang, L. Meng, S. Wang, Y. Lu, D. Ma, Activation of fibronectin/PI-3K/Akt2 leads to chemoresistance to docetaxel by regulating survivin protein expression in ovarian and breast cancer cells, Cancer Lett. 261 (2008) 108–119.
[53] M. Amrutkar, M. Aasrum, C.S. Verbeke, I.P. Gladhaug, Secretion of fibronectin by human pancreatic stellate cells promotes chemoresistance to gemcitabine in pancreatic cancer cells, BMC Cancer 19 (2019).

[54] E. Sahai, I. Astsaturov, E. Cukierman, D.G. DeNardo, M. Egeblad, R.M. Evans, D. Fearon, F.R. Greten, S.R. Hingorani, T. Hunter, R.O. Hynes, R.K. Jain, T. Janowitz, C. Jorgensen, A.C. Kimmelman, M.G. Kolonin, R.G. Maki, R.S. Powers, E. Pure, D.C. Ramirez, R. Scherz-Shouval, M.H. Sherman, S. Stewart, T.D. Tlsty, D. A. Tuveson, F.M. Watt, V. Weaver, A.T. Weeraratna, Z. Werb, A framework for advancing our understanding of cancer-associated fibroblasts, Nat. Rev. Cancer 20 (2020) 174–186.
[55] W.W. Du, L. Fang, X.L. Yang, W. Sheng, B.L. Yang, A. Seth, Y. Zhang, B.B. Yang, A. J. Yee, The role of versican in modulating breast cancer cell self-renewal, Mol. Cancer Res. 11 (2013) 443–455.
[56] A. Klejewski, K. Sterzynska, K. Wojtowicz, M. Swierczewska, M. Partyka, M. Brazert, M. Nowicki, M. Zabel, R. Januchowski, The significance of lumican expression in ovarian cancer drug-resistant cell lines, Oncotarget 8 (2017) 74466–74478.
[57] M.C. Boelens, T.J. Wu, B.Y. Nabet, B. Xu, Y. Qiu, T. Yoon, D.J. Azzam, C.T.-S. Victor, B.Z. Wiemann, H. Ishwaran, P.J. ter Brugge, J. Jonkers, J. Slingerland, A. J. Minn, Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways, Cell 159 (2014) 499–513.
[58] L. Lin, A.J. Sabnis, E. Chan, V. Olivas, L. Cade, E. Pazarentzos, S. Asthana, D. Neel, J.J. Yan, X. Lu, L. Pham, M.M. Wang, N. Karachaliou, M. Gonzalez Cao, J. Luis Manzano, J. Luis Ramirez, J.M. Sanchez Torres, F. Buttitta, C.M. Rudin, E. A. Collisson, A. Algazi, E. Robinson, I. Osman, E. Munoz-Couselo, J. Cortes, D. T. Frederick, Z.A. Cooper, M. McMahon, A. Marchetti, R. Rosell, K.T. Flaherty, J. A. Wargo, T.G. Bivona, The Hippo effector YAP promotes resistance to RAF- and MEK-targeted cancer therapies, Nat. Genet. 47 (2015) 250. -+.
[59] S.R. Datta, H. Dudek, X. Tao, S. Masters, H.A. Fu, Y. Gotoh, M.E. Greenberg, Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery, Cell 91 (1997) 231–241.
[60] O.N. Ozes, L.D. Mayo, J.A. Gustin, S.R. Pfeffer, L.M. Pfeffer, D.B. Donner, NF-kappa B activation by tumour necrosis factor requires the Akt serine-threonine kinase, Nature 401 (1999) 82–85.
[61] L.D. Mayo, D.B. Donner, A phosphatidylinositol 3-kinase/Akt pathway promotes translocation of Mdm2 from the cytoplasm to the nucleus, Proc. Natl. Acad. Sci. U. S.A. 98 (2001) 11598–11603.
[62] M.Y. Sun, G.F. Chi, J.J. Xu, Y. Tan, J.Y. Xu, S. Lv, Z.R. Xu, Y.H. Xia, L.S. Li, Y.L. Li, Extracellular matrix stiffness controls osteogenic differentiation of mesenchymal stem cells mediated by integrin alpha 5, Stem Cell Res. Ther. 9 (2018) 13.
[63] J.-L. Yu, H.-Y. Liao, Piezo-type mechanosensitive ion channel component 1 (Piezo1) in human cancer, Biomed. Pharmacother. 140 (2021).
[64] S. Tsukamoto, Y. Huang, D. Umeda, S. Yamada, S. Yamashita, M. Kumazoe, Y. Kim, M. Murata, K. Yamada, H. Tachibana, 67-kDa laminin receptor-dependent protein phosphatase 2A (PP2A) activation elicits melanoma-specific antitumor activity overcoming drug resistance, J. Biol. Chem. (2014) 289.
[65] M. Deng, J. Lin, S. Nowsheen, T.Z. Liu, Y.C. Zhao, P.W. Villalta, D. Sicard, D. J. Tschumperlin, S. Lee, J. Kim, Z.K. Lou, Extracellular matrix stiffness determines DNA repair efficiency and cellular sensitivity to genotoxic agents, Sci. Adv. 6 (2020) 15.
[66] L.R. Gomes, A.T. Vessoni, C.F.M. Menck, Three-dimensional microenvironment confers enhanced sensitivity to doxorubicin by reducing p53-dependent induction of autophagy, Oncogene 34 (2015) 5329–5340.
[67] S. Nishikawa, H. Ishii, N. Haraguchi, Y. Kano, T. Fukusumi, K. Ohta, M. Ozaki, D. Sakai, T. Satoh, H. Nagano, Y. Doki, M. Mori, Genotoxic therapy stimulates error-prone DNA repair in dormant hepatocellular cancer stem cells, Exp. Ther. Med. 3 (2012) 959–962.
[68] H. Cheng, Z. Zhang, R. Rodriguez-Barrueco, A. Borczuk, H. Liu, J. Yu, J.M. Silva, S. K. Cheng, R. Perez-Soler, B. Halmos, Functional genomics screen identifies YAP1 as a key determinant to enhance treatment sensitivity in lung cancer cells, Oncotarget 7 (2016) 28976–28988.
[69] B. Mao, F. Hu, J. Cheng, P. Wang, M. Xu, F. Yuan, S. Meng, Y. Wang, Z. Yuan, W. Bi, SIRT1 regulates YAP2-mediated cell proliferation and chemoresistance in hepatocellular carcinoma, Oncogene 33 (2014) 1468–1474.
[70] L.-h. Zhang, A.-j. Yang, M. Wang, W. Liu, C.-y. Wang, X.-f. Xie, X. Chen, J.-f. Dong, M. Li, Enhanced autophagy reveals vulnerability of P-gp mediated epirubicin resistance in triple negative breast cancer cells, Apoptosis 21 (2016) 473–488.
[71] D.C. Belisario, J. Kopecka, M. Pasino, M. Akman, E. De Smaele, M. Donadelli, C. Riganti, Hypoxia dictates metabolic rewiring of tumors: implications for chemoresistance, Cells (2020) 9.
[72] J.-J. Deng, W. Zhang, X.-M. Xu, F. Zhang, W.-P. Tao, J.-J. Ye, W. Ge, Twist mediates an aggressive phenotype in human colorectal cancer cells, Int. J. Oncol. 48 (2016) 1117–1124.
[73] S. Nam, V.K. Gupta, H.-p. Lee, J.Y. Lee, K.M. Wisdom, S. Varma, E.M. Flaum, C. Davis, R.B. West, O. Chaudhuri, Cell cycle progression in confining microenvironments is regulated by a growth-responsive TRPV4-PI3K/Akt-p27 (Kip1) signaling axis, Sci. Adv. 5 (2019).
[74] O. Govaere, J. Wouters, M. Petz, Y.-P. Vandewynckel, K. Van den Eynde, A. Van den Broeck, S. Verhulst, L. Dolle, L. Gremeaux, A. Ceulemans, F. Nevens, L.A. van Grunsven, B. Topal, H. Vankelecom, G. Giannelli, H. Van Vlierberghe, W. Mikulits, M. Komuta, T. Roskams, Laminin-332 sustains chemoresistance and quiescence as part of the human hepatic cancer stem cell niche, J. Hepatol. 64 (2016) 609–617.
[75] J.-P.J. Cosse, M. Ronvaux, N. Ninane, M.J. Raes, C. Michiels, Hypoxia-induced decrease in p53 protein level and increase in c-jun DNA binding activity results in cancer cell resistance to etoposide, Neoplasia 11 (2009), 976-U917.
[76] J. Albrengues, M.A. Shields, D. Ng, C.G. Park, A. Ambrico, M.E. Poindexter, P. Upadhyay, D.L. Uyeminami, A. Pommier, V. Kuttner, E. Bruzas, L. Maiorino, C. Bautista, E.M. Carmona, P.A. Gimotty, D.T. Fearon, K. Chang, S.K. Lyons, K. E. Pinkerton, L.C. Trotman, M.S. Goldberg, J.T.H. Yeh, M. Egeblad, Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice, Science 361 (2018) 1353. -+.
[77] C.G. Colpaert, P.B. Vermeulen, S.B. Fox, A.L. Harris, L.Y. Dirix, E.A. Van Marck, The presence of a fibrotic focus in invasive breast carcinoma correlates with the expression of carbonic anhydrase IX and is a marker of hypoxia and poor prognosis, Breast Cancer Res. Treat. 81 (2003) 137–147.
[78] Z.L. Liu, H.H. Chen, L.L. Zheng, L.P. Sun, L. Shi, Angiogenic signaling pathways and anti-angiogenic therapy for cancer, Signal Transduct. Targeted Ther. 8 (2023).
[79] W.A. Irwin, N. Bergamin, P. Sabatelli, C. Reggiani, A. Megighian, L. Merlini, P. Braghetta, M. Columbaro, D. Volpin, G.M. Bressan, P. Bernardi, P. Bonaldo, Mitochondrial dysfunction and apoptosis in myopathic mice with collagen VI deficiency, Nat. Genet. 35 (2003) 367–371.
[80] H. Koelbel, D. Hathazi, M. Jennings, R. Horvath, A. Roos, U. Schara, Identification of candidate protein markers in skeletal muscle of laminin-211-deficient CMD type 1A-patients, Front. Neurol. 10 (2019).
[81] R. Kalluri, The biology and function of exosomes in cancer, J. Clin. Invest. 126 (2016) 1208–1215.
[82] W.-x. Chen, X.-m. Liu, M.-m. Lv, L. Chen, J.-h. Zhao, S.-l. Zhong, M.-h. Ji, Q. Hu, Z. Luo, J.-z. Wu, J.-h. Tang, Exosomes from drug-resistant breast cancer cells transmit chemoresistance by a horizontal transfer of MicroRNAs, PLoS One 9 (2014).
[83] L. Qu, J. Ding, C. Chen, Z.-J. Wu, B. Liu, Y. Gao, W. Chen, F. Liu, W. Sun, X.-F. Li, X. Wang, Y. Wang, Z.-Y. Xu, L. Gao, Q. Yang, B. Xu, Y.-M. Li, Z.-Y. Fang, Z.-P. Xu, Y. Bao, D.-S. Wu, X. Miao, H.-Y. Sun, Y.-H. Sun, H.-Y. Wang, L.-H. Wang, Exosome-transmitted lncARSR promotes sunitinib resistance in renal cancer by acting as a competing endogenous RNA, Cancer Cell 29 (2016) 653–668.
[84] Y. Hu, C. Yan, L. Mu, K. Huang, X. Li, D. Tao, Y. Wu, J. Qin, Fibroblast-derived exosomes contribute to chemoresistance through priming cancer stem cells in colorectal cancer, PLoS One 10 (2015).
[85] D. Peng, M. Fu, M. Wang, Y. Wei, X. Wei, Targeting TGF-Beta Signal Transduction for Fibrosis and Cancer Therapy, Molecular Cancer, 2022, p. 21.
[86] C.S. Samuel, R.G. Bennett, Relaxin as an anti-fibrotic treatment: perspectives, challenges and future directions, Biochem. Pharmacol. (2022) 197.
[87] I. Caon, B. Bartolini, A. Parnigoni, E. Carava, P. Moretto, M. Viola, E. Karousou, D. Vigetti, A. Passi, Revisiting the hallmarks of cancer: the role of hyaluronan, Semin. Cancer Biol. 62 (2020) 9–19.
[88] L. Morosi, M. Meroni, P. Ubezio, I.F. Nerini, L. Minoli, L. Porcu, N. Panini, M. Colombo, B. Blouw, D.W. Kang, E. Davoli, M. Zucchetti, M. D'Incalci, R. Frapolli, PEGylated recombinant human hyaluronidase (PEGPH20) pre-treatment improves intra-tumour distribution and efficacy of paclitaxel in preclinical models, J. Exp. Clin. Cancer Res. 40 (2021).
[89] J.M. Yang, Z.D. Xu, H. Wu, H.G. Zhu, X.H. Wu, W.N. Hait, Overexpression of extracellular matrix metalloproteinase inducer in multidrug resistant cancer cells, Mol. Cancer Res. 1 (2003) 420–427.
[90] L.G.N. de Almeida, H. Thode, Y. Eslambolchi, S. Chopra, D. Young, S. Gill, L. Devel, A. Dufour, Matrix metalloproteinases: from molecular mechanisms to physiology, pathophysiology, and pharmacology, Pharmacol. Rev. 74 (2022) 712–768.
[91] H.R. Keiser, A. Sjoerdsma, Studies on beta-aminopropionitrile in patients with scleroderma, Clin. Pharmacol. Therapeut. 8 (1967) 593–+.
[92] S.A. Harrison, M.F. Abdelmalek, S. Caldwell, M.L. Shiffman, A.M. Diehl, R. Ghalib, E.J. Lawitz, D.C. Rockey, R.A. Schall, C. Jia, B.J. McColgan, J.G. McHutchison, G. M. Subramanian, R.P. Myers, Z. Younossi, V. Ratziu, A.J. Muir, N.H. Afdhal, Z. Goodman, J. Bosch, A.J. Sanyal, G.-U.- Investigators, Simtuzumab is ineffective for patients with bridging fibrosis or compensated cirrhosis caused by nonalcoholic steatohepatitis, Gastroenterology 155 (2018) 1140–1153.
[93] Y. Yao, A. Findlay, J. Stolp, B. Rayner, K. Ask, W. Jarolimek, Pan-Lysyl oxidase inhibitor PXS-5505 ameliorates multiple-organ fibrosis by inhibiting collagen crosslinks in rodent models of systemic sclerosis, Int. J. Mol. Sci. 23 (2022).
[94] R.J. Slack, S.J.F. Macdonald, J.A. Roper, R.G. Jenkins, R.J.D. Hatley, Emerging therapeutic opportunities for integrin inhibitors, Nat. Rev. Drug Discov. 21 (2022) 60–78.
[95] K.B. Kim, V. Prieto, R.W. Joseph, A.H. Diwan, G.E. Gallick, N.E. Papadopoulos, A. Y. Bedikian, L.H. Camacho, P. Hwu, C.S. Ng, W. Wei, M.M. Johnson, S. M. Wittemer, A. Vardeleon, A. Reckeweg, A.D. Colevas, A randomized phase II study of cilengitide (EMD 121974) in patients with metastatic melanoma, Melanoma Res. 22 (2012) 294–301.
[96] J.C. Dawson, A. Serrels, D.G. Stupack, D.D. Schlaepfer, M.C. Frame, Targeting FAK in anticancer combination therapies, Nat. Rev. Cancer 21 (2021) 313–324.
[97] A.M. Roy, R. Iyer, S. Chakraborty, The extracellular matrix in hepatocellular carcinoma: mechanisms and therapeutic vulnerability, Cell reports, Medicine 4 (2023), 101170-101170.
[98] S. Chakraborty, K. Njah, A.V. Pobbati, Y.B. Lim, A. Raju, M. Lakshmanan, V. Tergaonkar, C.T. Lim, W. Hong, Agrin as a mechanotransduction signal regulating YAP through the hippo pathway, Cell Rep. 18 (2017) 2464–2479.
[99] J.A. Prescott, J.P. Mitchell, S.J. Cook, Inhibitory feedback control of NF-B-K signalling in health and disease, Biochem. J. 478 (2021) 2619–2664.