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REVIEW
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Tumor-Associated Extracellular Matrix: How to Be a Potential Aide to Anti-tumor Immunotherapy?

Yingying He[1,2†], Tao Liu[1,3†], Shuang Dai[1†], Zihan Xu[1], Li Wang[1] and Feng Luo[1*]*

[1] Department of Medical Oncology, Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [2] Oncology Department, People's Hospital of Deyang City, Deyang, China, [3] Department of Oncology, The First Affiliated Hospital of Chengdu Medical College, Chengdu Medical College, Chengdu, China

The development of cancer immunotherapy, particularly immune checkpoint blockade therapy, has made major breakthroughs in the therapy of cancers. However, less than one-third of the cancer patients obtain significant and long-lasting therapeutic effects by cancer immunotherapy. Over the past few decades, cancer-related inflammations have been gradually more familiar to us. It's known that chronic inflammation in tumor microenvironment (TME) plays a predominant role in tumor immunosuppression. Tumor-associated extracellular matrix (ECM), as a core member of TME, has been a research hotspot recently. A growing number of studies indicate that tumor-associated ECM is one of the major obstacles to realizing more successful cases of cancer immunotherapy. In this review, we discussed the potential application of tumor-associated ECM in the cancer immunity and its aide potentialities to anti-tumor immunotherapy.

Keywords: extracellular matrix, cancer-immunity cycle, T-cell lymphocyte, immunotherapy, proteoglycans

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****Correspondence:***
Feng Luo
hxluofeng@163.com
Li Wang
wangli37029192@sina.com

† These authors have contributed equally to this work

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INTRODUCTION

The adaptative immune response protects against tumors (Ribas, 2015). However, neoplastic cells have developed strategies to avoid immune detection and elimination, that is considered as a hallmark of cancer (Hanahan and Weinberg, 2011). The therapeutic potential of host-versus-tumor effect can be motivated with novel immune therapies, including immune checkpoint inhibitors (ICIs), adoptive cell therapy, and vaccines (Baxevanis et al., 2009). $CD4^+$ and $CD8^+$ T lymphocytes comprise primary effector cells against tumors. Any step from the release of cancer cell antigens to the killing of cancer cells is regulated by several regulatory mechanisms. Immune checkpoints are inhibitory regulators that act as "breaks" on the immune response, which can be targeted by ICIs (Zhang and Zheng, 2020). Although a variety of ICIs have been significantly successful in cancer treatment, the curative effect remains poor (Li et al., 2019).

It is an urgent issue to solve the intrinsic and secondary resistance of ICIs. Herein, we have to mention ECM, a non-cellular three-dimensional macromolecular network composed of collagens, proteoglycans (PGs)/glycosaminoglycans (GAGs), elastin, fibronectin (FN), laminins, and several other glycoproteins (Theocharis et al., 2016). Whether in normal tissue or tumors, matrix components and cell adhesion receptors combine with each other to form a complex network where diverse cells reside. For many years, ECM was regarded as an inert cellular scaffold, which only provided structure for the cells. In the past two decades, people have discovered more functions that affect both biochemical and biophysical processes in cells, and ECM has been regarded as a reservoir and binding site of bioactive molecules (Brown, 2011). Cell surface receptors transmit signals from ECM to cells to regulate a variety of cell functions, such as survival, growth,

migration, differentiation and immunity, which are essential for maintaining normal homeostasis (Humphrey et al., 2014).

Essentially, ECM is a highly dynamic entity that continuously undergoes remodeling mediated by several matrix-degrading mechanisms during normal and pathological conditions (Lu et al., 2012; Yue, 2014). Continuous modification or dysregulation of ECM can lead to tumorigenesis (Walker et al., 2018). As far as we know, solid tumors characterized by disrupted tissue homeostasis and loss of differentiation phenotype are always accompanied by alterations in the composition, tissue and mechanical properties of the ECM (Eble and Niland, 2019). A large number of studies have shown that tumor-associated ECM is involved in promoting the growth, invasion, metastasis, and angiogenesis of tumor cells (Watanabe, 2010; He et al., 2016; Erdogan and Webb, 2017; Najafi et al., 2019), but it resists cell death and drug diffusion (Mason et al., 2017; Hwang et al., 2019).

In addition, a recent study showed that the remodeling of neoplastic ECM will regulate the immune system (Mohan et al., 2020), which is usually regarded as an obstacle to immune response (Vaday and Lider, 2000; **Figure 1**). Simply put, immune cells are actively involved in regenerating damaged tissues and promoting the deposition and formation of ECM (Pickup et al., 2014). In turn, the tumor-associated ECM contributes to the development of an immunosuppressive network, where cancer cells intertwine with fibroblasts, immune cells, endothelial cells, and other sorts of stromal cells. Within the newly formed network, secreted cytokines and chemokines can lead to immune escape of tumor (Nikitovic et al., 2014; Chakravarthy et al., 2018; Gao et al., 2019).

Up to now, the clinical trial data of cancer immunotherapy have confirmed that less than one third of the patients have a lasting and significant therapeutic effect (Wang et al., 2020). One of the predictors of therapeutic effect is tumor-infiltrating T cells, which are closely related to immune hot tumors or immune cold tumors. The hot tumors characterized by molecular markers of T cell infiltration and immune activation show a high response rate to immunotherapy such as anti-programmed death ligand 1 (PD-L1)/PD-1 therapy, whereas, cold tumors show striking features of T cell absence or exclusion (Gajewski, 2015; Zemek et al., 2019). Emerging evidence suggests that a common rate-limiting step is the immunostat function. Components in ECM and its proteolytic remodeling products can regulate the immune response, and act as an immune rheostat or "immunostat" (Pao et al., 2018). How does ECM affect the anti-tumor immunity? Will ECM be closely related to immune cold tumors? In view of these two issues, we will focus on the relationship between ECM and tumor immune response, and critically review the role of ECM in cancer immunity and its potential combination with cancer immunotherapy.

EXTRACELLULAR MATRIX IN CANCER

Extracellular matrix is an intricate network of extracellular-secreted macromolecules, such as collagens, enzymes and glycoproteins, with main functions dealing with structural scaffolding and biochemical support of cells and tissues (Lu et al., 2012). Generally, ECM can be divided into the basement membrane (BM) and the interstitial matrix (IM), to support epithelial/endothelial cell behavior and support the underlying stromal compartment and peri-cellular membrane, respectively (Theocharis et al., 2016). Degradation of the surrounding ECM is an essential part of the growth of invasive cancer, and it's also the main cause of destroying normal tissue (Madsen and Bugge, 2015). Most importantly, the degradation of ECM is accompanied by the deposition of a different tumor-specific ECM (Schedin and Keely, 2011), which usually increases in density and stiffness (Cox and Erler, 2014).

Basement Membrane

Basement membrane, composed of collagens, laminins, PGs, and FN (Haraida et al., 1996), sites at the interface between parenchyma and connective tissue, providing an anchoring sheet-like layer for parenchymal cells in order to be held together preventing them from being torn (Halfter et al., 2015). In epithelial cancers, BM acts as a structural barrier of invasion, intravasation and extravasation of cancer cells. During the development and progression of cancer, changes in BM are often observed. Generally, cancer cells invade the BM through such means as producing ECM remodeling enzymes (e.g., Matrix Metalloproteinases), using natural pores in BM, or forcing their way through those pores (Chang and Chaudhuri, 2019). In addition, a more complicated phenomenon is observed, that is, invasion also depends on the contact of cancer cells with collagen fibers in the underlying stroma (Nissen et al., 2019). In areas assembled by sheet-like arrangements of laminins (Gordon-Weeks et al., 2019), FN (Lin et al., 2019) as well as collagens I, III, and IV, the BM was excessively thickened (Nissen et al., 2019). This structural arrangement effectively divides the tumor into cancer cells nests and stromal regions, thereby producing the malignant behavior of cancer cells (Eble and Niland, 2019) and regulating tumor immune response (Vaday and Lider, 2000).

Interstitial Matrix

Under physiological condition, IM is a loose ECM that goes deep into the BM, which is composed of collagens I and III, elastin fibers and glycoproteins. Fibroblasts, resident immune cells, vasculature, and lymphatics are all embedded within it (Bruckner-Tuderman et al., 2010; Mecham, 2012). However, in some tumors, collagen fibers in IM are thicker, more organized and denser due to the increased deposition of collagen fibers (Drifka et al., 2016b; Nissen et al., 2019). With the development of cancers, stromal collagen fibers become increasingly aligned, particularly at the edge of cancers, thus promoting the invasion of cancer cell (Conklin et al., 2011; Burke et al., 2013; Han et al., 2016). Furthermore, lysyl oxidase (LOX) family catalyzes the formation of collagen cross-linking (Laczko and Csiszar, 2020). In tumors, the increased expression of LOX leads to excessive cross-linking of collagen, and at the same time, collagen deposition increases, increasing the stiffness, and leading to solid stress in the tumor (Choi et al., 2017). Besides the change of collagen, various glycoproteins in the ECM are also expressed pathologically, such as versican (VACN) and FN. All

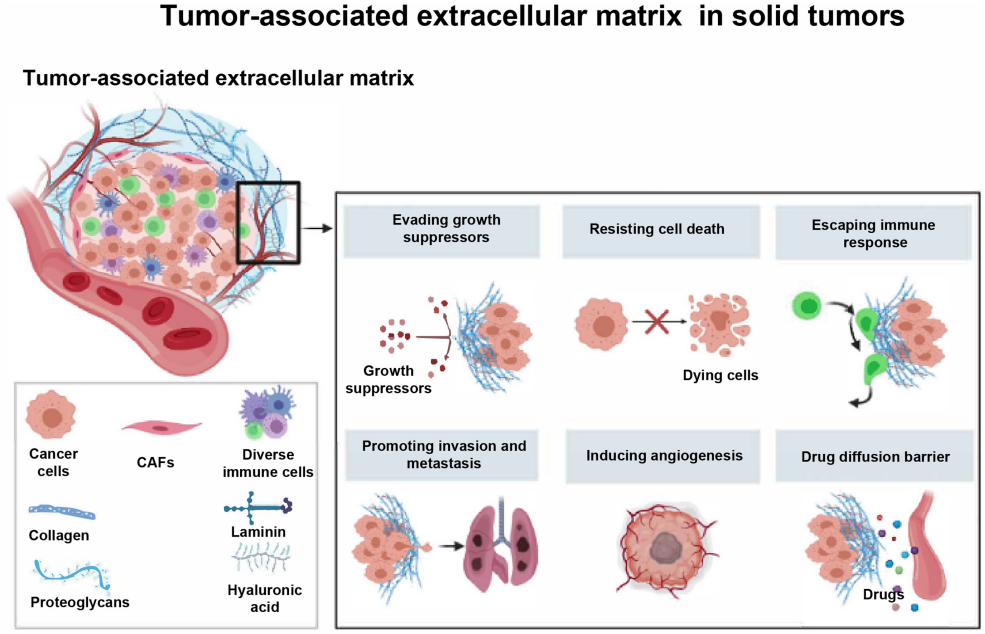

FIGURE 1 | The major components and roles of tumor-associated extracellular matrix in solid tumors. The tumor-associated ECM has been considered as a newly formed network that is essential for the protection of tumor cells and promotion of tumor progression. CAFs, cancer associated fibroblasts.

of them form a niche to facilitate cells migration, adherence and metastasis (Theocharis et al., 2016).

Major Components of Extracellular Matrix

Collagens

Collagen is one of the main components of ECM, which participates in cancer fibrosis and structural formation of solid cancers together with matrix glycoproteins, such as FN, laminins, elastin, and versican (Nissen et al., 2019). The biosynthesis of collagen is always regulated by fibroblasts, cancer cells and other stromal cells (e.g., macrophages) through mutated genes, transcription factors, multiple signaling pathways, and receptors (Sorushanova et al., 2019). Other substances in ECM, such as FN, hyaluronic acid (HA), laminin, and matrix metalloproteinases (MMPs), interact with collagen through integrins, discoidin domain receptors (DDR), tyrosine kinase receptors, and some signaling pathways to influence the behavior and activity of cancer cells. Changes of the internal matrix composition of cancer eventually form a mutual feedback loop, which affects the prognosis, recurrence and treatment resistance of cancer (Xu et al., 2019).

Several advanced stages of cancer, such as pancreatic cancer (Vennin et al., 2015), breast cancer (Nolan et al., 2020), colon cancer (Tabuso et al., 2021), are characterized by a desmoplastic reaction, which is manifested by extensive deposition of fibrillar collagens in ECM, presenting thicker, more organized and more highly packed collagen fibers. Deposition of these fibers leads to typical stiff matrix of cancer (Stylianopoulos et al., 2018), especially in the tumor regions nearby the BM, where increased fiber density can enhance the invasion of cancer cell (Jurmeister et al., 2020) and cause the poor prognosis of several cancers such as breast cancer (Bredfeldt et al., 2014), pancreatic cancer (Drifka et al., 2016a), gastric cancer (Ohno et al., 2002), and oral squamous cell carcinomas (Li et al., 2013).

Solid stress results from a combination of rapid proliferation of cancer cells, cell-ECM interactions and massive ECM deposition, all of which interact with resistive forces from the surrounding normal tissue (Löffek et al., 2016). Cancer cells sense these mechanical changes of the ECM through specialized transmembrane receptors including integrins (Cooper and Giancotti, 2019), DDRs (Coelho and McCulloch, 2018) and syndecans (Kang et al., 2018), and transform them into biological reactions to regulate cell functions.

Integrins are the main receptors of collagen, which are widely expressed and promote cell migration, and may be a key pathway for tumor angiogenesis, chemotherapy resistance, and metastasis (Naci et al., 2015; Zeltz and Gullberg, 2016; Wu et al., 2019). Integrin α11β1, a stromal cell-specific receptor for fibrillar collagens, is overexpressed in carcinoma-associated fibroblasts (CAFs). Non-small cell lung carcinoma (NSCLC) xenografts in α11 knockout ($\alpha11^{-/-}$) severe combined immune deficient (SCID) mice was significantly impeded, as compared with wild-type ($\alpha11^{+/+}$) SCID mice, which showed that collagen cross-linking was associated with stromal α11 expression, and the loss of tumor-stromal α11 expression was related to collagen reorganization and the decrease of stiffness (Navab et al., 2016). The forced expression of β1 integrin significantly stimulated Src and extracellular signal-regulated kinase (ERK) phosphorylation, increased cell stiffness, and accelerated cell motility, suggesting that the integrin signaling pathway activated in a tumor

environment with collagen deposition is responsible for low cell elasticity and high metastatic ability (Chen et al., 2014). Integrins also control local activation of transforming growth factor β (TGF-β) in ECM and cell-surface reservoirs. Integrin-dependent activation of TGF-β has become an important mechanism, through which tissue-borne cells guide circulating and resident immune cells (Nolte and Margadant, 2020). Therefore, specific inhibition of integrin-mediated cancer cell-collagen interaction may provide an opportunity for therapeutic intervention in the metastasis and spread of certain cancers like ovarian cancer (Huang et al., 2020).

In addition, DDRs (DDR1 and DDR2), non-integrin collagen receptors, are expressed on the surface of tumor cell, belonging to the receptor tyrosine kinase (RTK) family. DDRs show delayed and sustained activation when interacting with collagen (Orgel and Madhurapantula, 2019), and DDR-collagen signaling plays an important role in cancer proliferation and progression (Gadiya and Chakraborty, 2018). When DDR2 is activated, it will trigger a signaling cascade involving protein tyrosine phosphatase-2 (SHP-2), SRC, and MAP (mitogen-activated protein) kinases with SH2 domain. A study showed that knockdown of DDR2 in the NA13 cell line, B16F10 cell line and mammary tumor cell line E0771 could enhance the sensitivity of tumor cells to anti-PD-1 therapy *in vitro*. *In vivo*, tumor load reduction and higher $CD8^+$T cells infiltration in tumor were observed in tumor-bearing mice treated by dasatinib (a tyrosine kinase inhibitor of DDR2) plus anti-PD-1 (Tu et al., 2019). A clinical trial (NCT01643278) showed that dasatinib and ipilimumab can be safely administered to patients with gastrointestinal stromal tumor (GIST) and sarcoma. However, dasatinib was not synergistic with ipilimumab, as there was limited clinical efficacy with the combination (D'Angelo et al., 2017).

In addition to the above-mentioned effects of collagen, the relationship between collagen and tumor-associated macrophages (TAMs) in anti-tumor immunity should not be underestimated. TAMs, regarded as a major limitation for the efficacy of cancer immunotherapy, always suppress the activity of tumor-infiltrating T cells to support tumor growth (Ngambenjawong et al., 2017). Co-culture assays with primary T cells showed that macrophages cultured in high-density collagen had low efficiency in attracting cytotoxic T cells, and were capable of inhibiting T cell proliferation, which indicated that a high collagen density can guide macrophages to acquire an immunosuppressive phenotype (Larsen et al., 2020).

Proteoglycans

Proteoglycans, as components of ECM, play a key role in providing intrinsic signals needed to coordinate key events of regulating cancer immunity (Schaefer et al., 2017). PGs are complex molecules consisting of a protein core into which one or more glycosaminoglycan (GAG) chains are covalently linked (Piperigkou et al., 2016). The bound GAGs can be the heparan sulfate (HS), the chondroitin sulfate/dermatan sulfate (CS/DS) or the keratan sulfate (KS) (Iozzo and Schaefer, 2015). PGs are highly implicated in the processes of cancer-associated inflammation and regulate key events, respectively, to both innate and adaptive immunity (Schaefer et al., 2017). In this section, we will list three members of PGs that have been deeply studied. Other members may appear in other sections.

Versican, a member of the hyalectan family of large chondroitin sulfate PGs (CSPGs), has been proved to be overexpressed in many cancers (Papadas et al., 2020). VCAN can act as a tissue "landing strips" for inflammatory cells from the circulation via binding tumor necrosis factor stimulated gene-6 (TSG-6) and inter alpha trypsin inhibitor (IαI) (Wight et al., 2014). In addition, VCAN interacts with inflammatory cells either indirectly via HA or directly via receptors such as CD44, P-selectin glycoprotein ligand-1 (PSGL-1) and toll-like receptors (TLRs), and activates signaling pathways to promote the synthesis and secretion of inflammatory cytokines such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), and nuclear factor kappa B (NFκB) (Kim et al., 2009; Wight et al., 2014).

Biglycan (BGN), a member of small leucine rich PGs (SLRPGs) (Schaefer et al., 2017), is overexpressed and secreted by various cancers (Wang et al., 2011; Liu et al., 2014; Fujiwara-Tani et al., 2020), which is related to the regulation of immunological responses (Neill et al., 2015). However, the oncogenic or tumor suppressive potential of BGN remains unclear. Compared to $BGN^{low/neg}$ HER-2/neu^+ fibroblasts, BGN^{high} HER-2/neu^+ fibroblasts were less tumorigenic and had increased immunogenicity in immune competent mice, possibly due to upregulation of major histocompatibility complex (MHC) class I surface antigens and reduced expression levels of TGF-β isoforms and TGF-β receptor 1 (Subbarayan et al., 2018). Soluble BGN activates the primary reaction of adaptor molecule myeloid differentiation 88 (MyD88), recruits neutrophils and macrophages by using the Toll like receptor 2/4 (TLR2/4) signaling pathways, or activates the domain-containing adaptor of Toll/interleukin 1R (IL-1R), and induces the activity of interferon β (IFN-β) recruited by T-lymphocyte (Zeng-Brouwers et al., 2014).

In addition to VCAN and BGN, HS proteoglycans (HSPGs) play a multifunctional role in inflammation, such as modulating multiple steps in the cascade of leukocyte recruitment (Kumar et al., 2015), activating lymphocytes (Wrenshall et al., 1994), and inducing phenotypic maturation of murine immature dendritic cells (DCs) with upregulation of I-A, CD40, CD54, CD80, and CD86 (Kodaira et al., 2000). El Ghazal et al. (2016) found that targeting of DC glycan sulfation through mutation in the heparan sulfate biosynthetic enzyme N-deacetylase/N-sulfotransferase-1 (Ndst1) in mice ($Ndst1^{f/f}$ $LysMCre^+$) increased DC maturation and inhibited trafficking of DCs to draining lymph nodes, and Lewis lung carcinoma tumors of $Ndst1^{f/f}$ $LysMCre^+$ mice were reduced in size (El Ghazal et al., 2016).

Glycosaminoglycans

Hyaluronic acid is a simple linear and unsulfated GAG composed of repeating units of N-acetylglucosamine (GlcNAc) and glucuronic acid (GlcUA), which is accumulated in a variety of human solid tumors (Nikitovic et al., 2015; Caon et al., 2020). The biological activities of HA depend on its molecular weight and the receptors interacting with it (Monslow et al., 2015). HA is initially synthesized as high molecular weight (HMW) polymers

beyond 500 kDa. These HMW-HA functions are mediated by constitutively expressed receptors, including CD44, lymphatic endothelial receptor (LYVE-1) and HA receptor for endocytosis (HARE) (Du et al., 2013) to maintain homeostasis and restrain cell proliferation and migration in normal tissues (Mueller et al., 2010; Tian et al., 2013). HMW-HA can be fragmented into low molecular weight (LMW) polymers between 7 and 200 kDa by hyaluronidases and free radicals (D'Agostino et al., 2015). These LMW-HA can promote inflammation, immune cell recruitment and epithelial cell migration (Törrönen et al., 2014; Litwiniuk et al., 2016). These functions are mediated by receptors for HA-mediated motility (RHAMM) and TLR2/4, which coordinate signaling with CD44 and other HA receptors (Misra et al., 2015). Elevated HMW-HA production in the absence of fragmentation is linked to cancer resistance, however, tumor cells always promote HA fragmentation associated with driving and maintaining malignant progression (Liu M. et al., 2019). For instance, fragmentated HA activates RhoGTPase signaling, rapamycin (mTOR) pathway and CDC42 signaling by binding CD44 to maintain proliferative signaling (Mattheolabakis et al., 2015; Skandalis et al., 2019).

The components mentioned above are only a small population of thousands of ECM components. They not only perform their respective functions, but also interact with each other and participate in the dynamic changes of ECM and immune response. In this article, we have discussed certain aspects in, such as how they affect the cancer-immunity cycle.

THE CANCER-IMMUNITY CYCLE AND ANTI-TUMOR IMMUNOTHERAPY

According to the theory of immune surveillance, cells and tissues are constantly under the control of the immune system (Ribatti, 2017). Cancer is a systemic disease, with prolonged inflammation as a hallmark (Singh et al., 2019). T immune system serves as a hindrance to cancer formation and progression, actively participating in resisting or eradicating the formation and progression of incipient cancer, advanced tumors, and micro-metastases (Abbott and Ustoyev, 2019). However, both extrinsic and intrinsic cancer inflammations can result in immunosuppression, thereby providing a preferred background for tumor development (Nakamura and Smyth, 2017).

Anti-tumor immunotherapy aims to combine with the host immune system to initiate or reinitialize a self-sustaining cycle of cancer immunity, so as to generate effective anti-tumor immune responses. In order to effectively kill cancer cells, it is necessary to initiate and repeat several stepwise events (Chen and Mellman, 2017). The steps are summarized as the cancer-immune cycle (**Figure 2**). In summary, there are 7 steps. Step 1, the antigens of tumorigenic cancer cell are released and captured by antigen-presenting cells (APCs). Step 2, the captured antigens are presented to T cells on MHC I and MHC II molecules by APCs. Step 3, the response of effector T cells (T_{EFF}) against the cancer-specific antigens is initiated and activated, and then T_{EFF} is amplified. Step 4, the activated T_{EFF} migrate toward tumors. Step 5, the activated T_{EFF} arrive at lesions and infiltrate the tumor bed. Step 6, activated T_{EFF} specifically recognize and bind cancer cells through the interactions between T cell receptor (TCR) and their homologous antigens bound to MHC I. Step 7, these activated T_{EFF} finally kill their target cancer cells through releasing perforin, granzyme, and interferon-gamma (IFN-γ). In this step, additional cancer cell antigens are released, which can restart step 1 again and strength the response in continuous rotation of the cycle (Chen and Mellman, 2013). However, negative feedback exists in cancer-immunity cycle, such as immune checkpoints (Kong, 2020), arginase (Caldwell et al., 2018) and vascular endothelial growth factor (VEGF) (Fukumura et al., 2018), preventing amplification of continued immune signals, and inhibiting or arresting the anticancer immune response. Several immune escape mechanisms have been described in many studies, including the lack of tumor-antigen recognition (Salzer et al., 2020), the resistance to cell death (Galluzzi et al., 2018), and the production of immunosuppressive molecules by tumor cells (Jie et al., 2013).

Unfortunately, only a few cancer patients can do very well in the cancer-immunity cycle, and a significant fraction of patients manifests innate or acquired resistance to those therapies (Galluzzi et al., 2018). A better understanding of resistance mechanisms depicts a central goal to avoid or overcome immunotherapy resistance, thereby improving the outcome of cancer patients. TME is a mechanism of resistance other than tumor cells themselves (Darragh et al., 2018; Horvath et al., 2020). ECM is the non-cellular stroma of TME, which hosts tumor cells, endothelial cells, mesenchymal cells, and various immune cells (Arneth, 2019). Growing research has shown that the remodeling of ECM plays an important role in shaping the inflammation and immune milieu of the tumor. The remodeling of ECM cytoskeleton, structural plasticity and mechanical forces are crucial factors for the transportation, activation, and formation of immunological synapses (Huse, 2017).

MULTIPLE ROLES OF EXTRACELLULAR MATRIX IN REGULATING THE CANCER-IMMUNITY CYCLE

As mentioned above, each step of the Cancer-Immunity Cycle requires the coordination of numerous factors, both stimulatory and inhibitory in nature (Chen and Mellman, 2017). According to current research results, ECM is able to participate in the regulation of multiple steps in the Cancer-immune Cycle, however, the results are scattered and not generalized. In order to have a more systematic and comprehensive understanding of the impacts of ECM on the cancer-immunity cycle, we will summarize them in the order of the steps of this cycle.

Stiff Extracellular Matrix Inhibits Cancer Cell Death and Decreases Release of Cancer Cell Antigens

Extracellular matrix in tumors is approximately at least 1.5-fold stiffer than that in the surrounding normal tissue (Najafi et al., 2019). By applying physical forces through the stiffened ECM

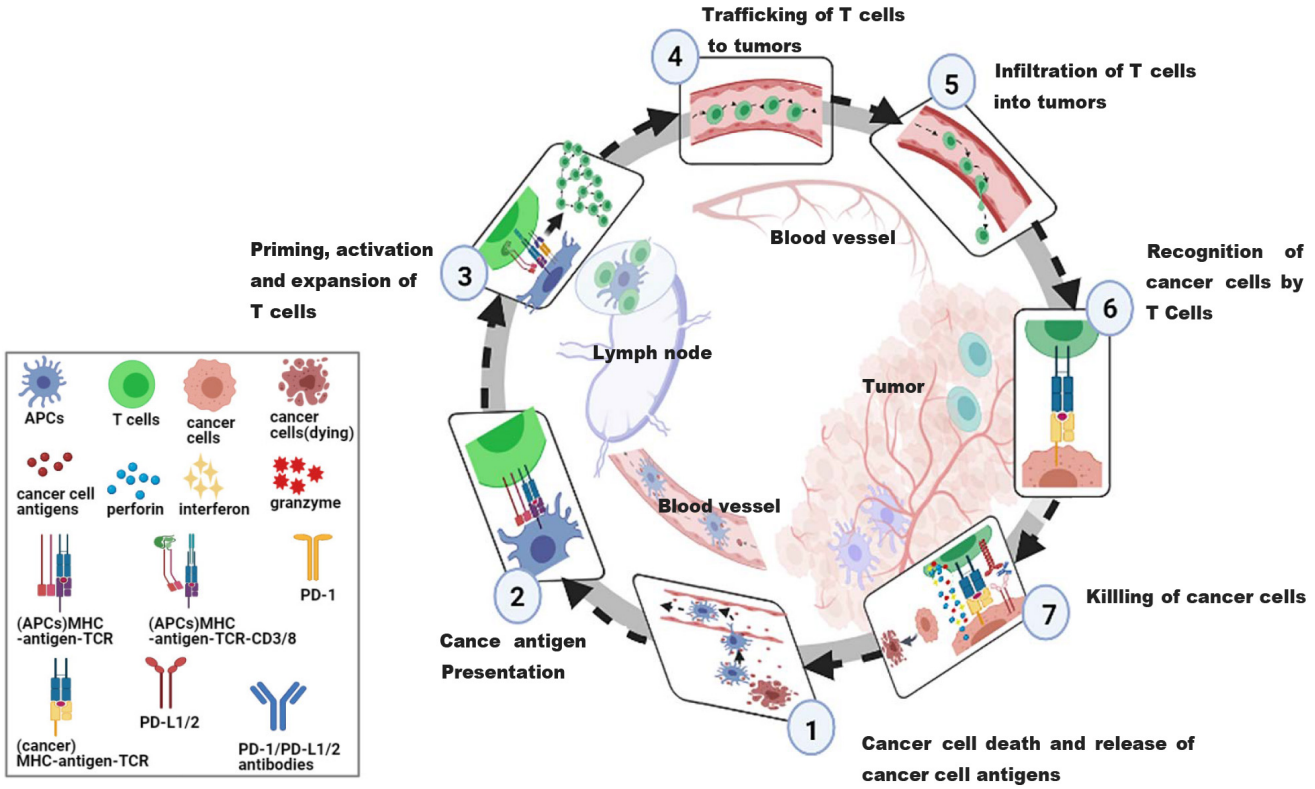

FIGURE 2 | The cancer-immunity cycle. An effective anticancer immune response is a cyclic process, theoretically, which can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the killing of cancer cells. Importantly, these steps must be repeated to amplify and broaden T cell responses. Each step is described as above, with the primary cell types involved and the anatomic location of the activity listed. APCs, antigen presenting cells, a type of cell in the body that takes up, processes and transmits antigenic information, and induces an immune response from T and B cells; MHC, major histocompatibility complex, involved in antigen presentation and the associated immune response, divided into MHC I and MHC II; MHC I, responsible for presenting viral, tumor or parasitic antigens; MHC II, responsible for initiating the immune response in bacterial infections; TCR, T cell receptor, an antigen receptor on the surface of T cells that recognizes pMHC complex; PD-1, programmed cell death protein 1, located on the surface of T cells and primary B cells; PD-L1/2, programmed cell death 1 ligand 1/2, ligand for PD-1.

on host tissues, tumors can enhance cell-ECM adhesion and break cell-cell contacts, leading to its growth (Dupont, 2016; Gkretsi and Stylianopoulos, 2018) and survival (Piersma et al., 2020). Inducing collagen cross-linking in a stiff ECM can enhance phosphoinositide 3-kinase (PI3K) activity, which improves the viability of cancer cells (Gao et al., 2020). Survival of cancer cells is also affected by the release of metalloproteinases (MMPs) from cells (Grzelczyk et al., 2016). MMPs, a family of proteolytic enzymes, degrade multiple components of ECM (Winer et al., 2018) and interact with integrins, thus promoting the survival of intracellular signal transducer and activator of transcription 3 (STAT3) (Najafi et al., 2019). HA activates RhoGTPase signaling, mTOR pathway and CDC42 signaling by binding CD44 to maintain proliferative signaling (Mattheolabakis et al., 2015; Skandalis et al., 2019). Moreover, ECM stiffness is indirectly involved in activation of ERK pathway, which contributes to the proliferation of cancer cells (Paszek et al., 2005).

As we all know, chemotherapeutic agents are always used to endow tumor cells with immunogenicity and/or increase their immunogenicity by inducing the death of immunogenic cell, thus increasing the release of cancer cell antigens (Garg et al., 2017; Wang et al., 2018). However, in addition to promoting survival of cancer cells by ECM, the stiffness of ECM is an obstacle to the effective uptake or delivery of drugs to the intratumoral area (Kaylan et al., 2016). In short, the enhancement of survival potential of tumor cells leads to their freedom from growth inhibition, which also reduces cell death and the release of cancer cell antigens (Gubin et al., 2015). As the first and key step for initiating anticancer immunity (Kroemer et al., 2013), a reduction in cancer cell antigen release will cripple the Cancer-Immunity Cycle.

Extracellular Matrix Interferes With Cancer Antigen Presentation

The functional basis for ICIs response is the immunogenicity of a tumor, which is mainly determined by tumor antigenicity and the efficiency of antigen presentation (Wang et al., 2019). APCs, including macrophages, DCs and B cells, are responsible for presenting antigens and triggering immunity by different mechanisms (Blander et al., 2017). DCs are the sentinel APCs of the immune system and act as initiators of antigen-specific T cell

responses (Constantino et al., 2017). Nevertheless, only mature DCs are able to induce anti-tumoral immunity, while antigens presented by immature DCs may lead to immune tolerance and fail to induce a T-cell response (Wculek et al., 2020).

It's worth noting that the ultimate fate of DC functions is determined by signals from the microenvironment (Leenman et al., 2010). ECM components might induce a DC phenotype with low immunogenicity (Sprague et al., 2011). Studies on the angiogenic and immune profile of murine myeloid DCs upon interaction with laminins (a family of large molecular weight glycoproteins) environments have shown that murine ovarian tumors produce several types of laminins and that DCs cultured on those laminins upregulate both AKT and MEK signaling pathways and decrease the immunological capacities, which contributes to their complicity in tumor growth (Aumailley, 2013; Phillippi et al., 2020). As mentioned in the second section, some matrix components, such as HS and HA, have immunoregulatory properties in experimental models. In mice, targeting the sulfation of HS on DCs through mutation in the heparan sulfate biosynthetic enzyme N-deacetylase/N-sulfotransferase-1 (Ndst1) can endow DCs with increased maturation and reduced chemokine-dependent trafficking to draining lymph nodes (El Ghazal et al., 2016), where mature DCs present the peptide to naive T cells in a complex with MHC proteins to initiate downstream reactions (Jakubzick et al., 2017).

Besides HS, HA can also regulate the maturation of DCs in a TLR4 dependent manner (Termeer et al., 2002). It was found that the exposure of DCs to HA fragments increased the expression of activation markers as MHC II, CD80, CD86, and CD40, and promoted DCs activation (Alaniz et al., 2009). When activated, DCs migrate to the draining lymph nodes and present the antigen to naive T cells (Worbs et al., 2017). Furthermore, HA can form provisional matrices with VACN. The HA-VACN interaction is important for the recruitment of inflammatory cells including neutrophils, macrophages and T cells (Andersson-Sjoland et al., 2015; Wight, 2017). The interaction between FN (a large glycoprotein of ECM) and integrin β1 in macrophages can promote TLR 2/4 signaling pathways to enhance expression of pro-inflammatory mediators and phagocytosis by macrophages (Fei et al., 2018). When located near the proximity of dying cancer cell, DCs together with macrophages can mobilize to lymphoid organs and present tumor antigens to adaptative immune cells, thus enabling the resolution of the tumor (Gardner and Ruffell, 2016).

Extracellular Matrix Influences the Initiation and Activation of Effector T Cells

Generally, naive T cells are located within lymph nodes to encounter with antigen-loaded DCs and be activated (Groom, 2015). In lymphoid nodes (LNs), various stromal cell subsets create dense 3D cellular networks, which provides the opportunity for naive T cells to interact with antigens presented by DCs, resulting in the initiation of an immune response (Mempel et al., 2004). The ultimate fate of T cell in LNs is determined by interactions with the matrix framework and various other immune components (Bousso and Robey, 2003). Fibroblastic reticular cells (FRCs), lymphatic endothelial cells (LECs), and blood endothelial cells (BECs) are the main LN stromal cells (SCs) (Fletcher et al., 2015). FRCs provide the three-dimensional scaffold in the LN niche, and are characterized by expressing podoplanin (gp38) and ECM proteins, such as laminins and collagens (Martinez et al., 2019). In the LN paracortex, collagen fibers, laminins and FRCs make up microchannels known as the conduit network. The conduit center has abundant collagen type I; the BM is rich with laminin α4β1γ1 (411), laminin α5β1γ1 (511), collagen type IV, and FN (Katakai et al., 2004). Bridging the subcapsular sinus and high endothelial venules (HEVs) by the conduit allows small molecules less than 70 kilodaltons, such as soluble antigens, chemokines and cytokines, to be delivered into the paracortex (Gretz et al., 2000; Roozendaal et al., 2008).

In LNs, immunity or tolerance induction can affect the expression of laminin α4 and α5 in all SCs (Warren et al., 2014). In response to immunity and inflammation, laminin α5 is upregulated (Li et al., 2020). On the contrary, α4 increases for tolerance induction. Functionally, laminin 411 and laminin 511 serve as co-inhibitory and co-stimulatory ligands for $CD4^+$ T cells, respectively. Laminin 411 inhibits the activation of $CD4^+$T cells and the polarization of Th1, Th2, and Th17, but facilitates the induction of polarization of T regulatory cells (iTreg). Laminin 511 is recognized by $CD4^+$ T cells through α6 integrin and α-dystroglycan to inhibit T cells activation, proliferation and differentiation (Simon et al., 2019).

T cells are initiated and activated in the tumor draining lymph nodes (TDLNs), and obtain their effector functions to migrate toward the tumor (Rotman et al., 2019). Interactions of T cells with major ECM structural components within TDLNs can regulate the function of T cells. In the T cell zone, FRCs support naive $CD4^+$ and $CD8^+$ T cell or memory precursor effector cell homeostasis by producing IL-7, IL-15, and CCL19. Moreover, the presentation of antigens linked to a stiff surface has been demonstrated to impair TCR-mediated T cell activation, suggesting that TCR is affected by mechanical force (O'Connor et al., 2012; Saitakis et al., 2017; Zhang et al., 2021).

Extracellular Matrix Regulates Immigration of T Cells, Including Trafficking and Infiltration to Tumors

Effector T cells from LNs to the tumor site are critical for the density and diversity of tumor-infiltrating T cells, which is closely related to the prognosis and curative effect of cancer immunotherapies (Bindea et al., 2013). This view is accepted as immune hot/cold tumors (Bonaventura et al., 2019). The process of T-cell trafficking is highly dynamic and governed by a complex array of mechanisms, involving complex interactions between T cells and endothelial cells (ECs) (Vaday and Lider, 2000; Vaday et al., 2001). In brief, during this process, T cells need toattach to the endothelium for a short time at first, then roll, firmly adhere and are activated on the endothelial surface, and finally extravasate through the blood vessel wall to tumor site (Masopust and Schenkel, 2013; Chimen et al., 2017).

T-cell trafficking is also highly dependent on microenvironmental clues. T cells utilize the porous three-dimensional ECM as a scaffold for both integrin-dependent and receptor-independent amoeboid motility (Jiang et al., 2016). Laminins can act as ligands that bind immune cell membrane receptors (mainly integrins) and initiate integrin-mediated signaling. In LNs, the vascular and lymphatic systems that support T cells trafficking are surrounded by BM which contains two laminin isoforms, laminin 411 and laminin 511 (Simon et al., 2019).

Stiff ECM may act as a physical barrier to T cells infiltration into the tumors and affect the preferential localization of T cells. For example, matrix density and architecture induced the localization and migration of T cells into the tumor stroma rather than into tumor cell nest in both pancreatic ductal adenocarcinoma (PDAC) and lung cancer model due to the impaired ability of T cells to infiltrate from the stroma to cancer cell nests (Salmon et al., 2012; Wolf et al., 2013; Hartmann et al., 2014). In contrast, loose areas of FN and collagen tend to facilitate the motility of T cells (Wolf et al., 2013).

Besides the rigidity, certain ECM components can also play a role in modulating the motility of T cells (He and Baum, 2004; O'Connor et al., 2012). The dense collagen-rich ECM has direct and indirect effects on the infiltration and function of T cells. In a three-dimensional cell culture systems without chemokine gradients, T cells move along the fibrillar collagen network in a process independent of integrin or protease activity. When activated $CD8^+$ T cells are encapsulated in collagen hydrogels with distinct fiber alignment, $CD8^+$ T cells move along the axis of collagen alignment, and faster and more persistently in aligned collagen fibers than in non-aligned collagen fibers (Pruitt et al., 2020). Additionally, when naive T cells are activated and become T_{EFF} in LNs, T_{EFF} express high levels of CD44 and can bind to HA. CD44 and its engagement with HA skews $CD8^+$ T cells toward a terminal effector differentiation state that reduces their ability to form memory cells. As T cell activation proceeds, HA binding increases, and the ability of T cells to roll on HA substrate is improved, which is quite important for the migration and extravasation of T cells (Vogt Sionov and Naor, 1997; Johnson and Jackson, 2021).

Extracellular Matrix Disturbs the Recognition and Killing of Cancer Cells by T Cells

It is generally believed that $CD8^+$ T cells are the main effector cells involved in the killing of cancer cells. Furthermore, killing cancer cells always follows the "recognition" step. In various cancers, collagen fibers are thicker and more closely packed around cancer cell nests than tumor stroma. The stiff ECM can serve as a space barrier surrounding tumor cells and limiting the accessibility by the $CD8^+$ T cells, which disturbs the recognition (Stromnes et al., 2015).

Spatial analysis of cancers demonstrates that cancers with excessive ECM deposition are resistant to immune checkpoint inhibition (Mariathasan et al., 2018), which is confirmed by data from multiple lung cancer patients (Peng et al., 2020). Collagen-induced $CD8^+$ T cell exhaustion is due to the leukocyte-specific collagen receptor 1 (LAIR1), which suppresses lymphocytic activity through SH2 domain-containing phosphatase 1 (SHP-1) signaling and is expressed on $CD8^+$ T cells following integrin beta 2 (CD18) binding to collagen (Lebbink et al., 2007). Reduction in tumor collagen deposition through Lysyl oxidase-like 2 (LOXL2) suppression increases T cell infiltration, diminishes exhausted T cells and abrogates resistance to anti-PD-L1 (Peng et al., 2020). Collagen density reduces the proliferation and tumoricidal activity of tumor-infiltrating T cells. Whole-transcriptome analysis of 3D-cultured T cells revealed that a high-density matrix induces downregulation of cytotoxic activity markers (CD101) and upregulation of regulatory T cell markers (CIP2A). These transcriptional changes have been predicted to involve autocrine TGF-β signaling and they are accompanied by an impaired ability of tumor infiltrating T cells to kill autologous cancer cells (Kuczek et al., 2019).

What's more, the expression of programmed death-ligand 1 (PD-L1) in tumor cells plays an important role in escaping from the "killing" step (Sun et al., 2018). A stiff substrate enhances the expression of PD-L1 in lung cancer cells through the actin-dependent mechanism, indicating that stiffness as a tumor environment can upregulate the expression of PD-L1 and lead to the escape of the immune system and tumor growth (Miyazawa et al., 2018; Azadi et al., 2019). Researchers are inspired by the effect of tumor-associated ECM on the cancer-immunity cycle stated above. If the negative effect of ECM is eliminated, the anti-tumor immunity would be significantly improved, thus achieving good immunotherapy effect and finally improving overall survival. Therefore, in the next section, we make a summary of strategies to eliminate the negative effect of ECM.

STRATEGIES TO MANIPULATE THE TUMOR-ASSOCIATED EXTRACELLULAR MATRIX

As a vast repository of anticancer targets, ECM has been a hot topic in recent decades (Lorusso et al., 2020), however, the potential for targeting the matrix to promote tumor immunity is less well recognized. The tumor-associated ECM can be therapeutically targeted in a number of ways, including targeting ECM molecules, ECM-remodeling enzymes, altering the structural or physical properties of the matrix, or regulating the fibroblast function as an indirect method to alter ECM deposition (Gordon-Weeks and Yuzhalin, 2020). In the following, we highlight a number of major therapeutic candidates for theregulation of ECM related to cancer immunity.

Strategies to Directly Target Extracellular Matrix Components

As aforesaid, the components of ECM can act as endogenous mediators of cancer-associated inflammation, which emerges a novel idea that immunosuppression can be improved by

targeting them. For instance, some studies demonstrates that the rationality of the modulation of PG's activities could be a novel approach in the field of cancer immunotherapy. The administration of versikine, a VCAN fragment of bioactive damage-associated molecular pattern, facilitates immune sensing of myeloma tumors and enhances T-cell-activating immunotherapies (Hope et al., 2016). The non-glycanated mouse or human endocan polypeptide (previously known as endothelial cell specific molecule-1, ESM-1) restrains tumor growth by increasing leukocyte infiltration *in vivo* and enhancing innate immunity response (Yassine et al., 2015). The modulation of Syndecans-1 (SDC1) expression could facilitate immunosurveillance and the resolution of precancerous lesions (Handra-Luca, 2020). It has been proved that BGN can bridge innate immunity with adaptive immunity through TLR2/4 downstream signaling because it has the ability to regulate the activities of neutrophils, macrophages, T lymphocytes, B lymphocytes, and DCs (Moreth et al., 2012). Conjugation immune checkpoint antibodies to the heparin binding domain (HBD) of placental growth factor-2 (PIGF-$2_{123-144}$) shows exceptionally high affinity for multiple ECM proteins. Peri-tumoral injection of PIGF-$2_{123-144}$-anti-PD-L1 leads to higher retention within tumor tissue. More than the high efficacy, it reduces systemic toxicity in the B16F10 melanoma model (Ishihara et al., 2017).

Accumulation of excessive HA can lead to the increase of interstitial pressure and impair the perfusion and chemotherapy delivery of tumors (Jacobetz et al., 2013). In preclinical studies, pegvorhyaluronidase alfa (PEGPH20), a pegylated recombinant human hyaluronidase, has been proved to successfully degrade HA in tumors and remodel the tumor stroma, thus improving perfusion and drug delivery. Therefore, the recent phase II HALO-202 clinical trial (NCT 01839487) showed that treatment with PEGPH20 plus gemcitabine and Nab-paclitaxel significantly improved progression-free survival (PFS) in patients with previously untreated metastatic PDAC (Hingorani et al., 2018). However, the phase III trial suggested that the addition of PEGPH20 to gemcitabine and Nab-paclitaxel increased the ORR but did not improve OS, which did not support further development of PEGPH20 in metastatic PDAC (Van Cutsem et al., 2020). The depletion of HA by hyaluronidase not only improves chemotherapy delivery, but it may also improve the success of immunotherapy, which has been demonstrated by animal models. Moreover, hyaluronidase (HAase) is employed to increase tumor tissues permeability by breaking down the HA in the ECM of tumors to enhance the tumor infiltration of the nanovaccine-generated tumor-specific T cells (Guan et al., 2018). In the presence of hyaluronidase, the delivery of both nano-vaccines and therapeutic monoclonal antibodies has been enhanced (Blair et al., 2019; Clift et al., 2019).

Similarly, collagen I targeting of cetuximab, an anti-EGFR monoclonal antibody, shows promising therapeutic efficacy in the A431 epidermoid cancer model (Liang et al., 2016). Cetuximab can retain a longer period in the collagen-rich tumors without loss of potency (Magdeldin et al., 2014). Collagen affinity also can be used to mediate targeted immunotherapy antibodies, for example, cancer-collagen-targeting immunoconjugate therapy (Katsumata et al., 2019). Fusion of the collagen-binding protein lumican and cytokines increases the efficacy of systemic immunotherapies in a melanoma model. ICIs and interleukin-2 (IL-2) by conjugation (for antibodies) or recombinant fusion (for cytokine) to the von Willebrand factor A3 domain (a collagen-binding domain) eradicated tumors and exhibited obvious safety and efficacy in a breast cancer model (Ishihara et al., 2019).

TABLE 1 | Examples of clinical trials combining agents targeting the tumor ECM with immunotherapy.

Target	Agent	Cancer	Plus immunotherapy	NIH number	Trial phase	Status/conclusion
FAK	Defactinib	Pancreatic Cancer	Pembrolizumab	NCT03727880	2	Recruiting
	Defactinib	Advanced solid tumors	Pembrolizumab	NCT02758587	1 and 2	Recruiting
	Defactinib	Advanced solid tumors	Pembrolizumab	NCT02546531	1	Completed
	Defactinib	Pleural mesothelioma	Pembrolizumab	NCT04201145	1	Withdrawn
	Defactinib	Epithelial ovarian cancer	Avelumab	NCT02943317	1	Withdrawn
Collagen	losartan	Localized pancreatic cancer	Nivolumab	NCT03563248	2	Recruiting
	Cetuximab	Squamous cell carcinoma of the head and neck	Monalizumab	NCT04590963	3	Recruiting
	Cetuximab	Recurrent/metastatic squamous cell carcinoma of the head and neck	Pembrolizumab	NCT03082534	2	Recruiting
Hyaluronan	PEGPH20	NSCLC and gastric cancer	Pembrolizumab	NCT02563548	1	Completed
	PEGPH20	Metastatic pancreatic cancer	Pembrolizumab	NCT04058964	2	withdrawn
	PEGPH20	HA high metastatic PDAC	Pembrolizumab	NCT03634332	2	Unknown
	PEGPH20	Advanced intrahepatic and extrahepatic cholangiocarcinoma and gallbladder adenocarcinoma	Atezolizumab	NCT03267940	1	Terminated
	PEGPH20	Resectable PDAC	Atezolizumab	NCT03979066	2	Terminated
	PEGPH20	Chemotherapy resistant pancreatic cancer	Avelumab	NCT03481920	1	Terminated
FAP	Talabostat	Advanced and recurrent solid cancer	Pembrolizumab	NCT04171219	2	Recruiting
DDR2	Dasatinib	Advanced non-small cell lung cancer	Nivolumab	NCT02750514	2	Terminated
	Dasatinib	Gastrointestinal stromal tumors or other sarcomas	Ipilimumab	NCT01643278	1	Completed

FAK, focal adhesion kinase, FAP, fibroblast activation protein, DDR2, discoidin domain receptors 2.

Strategies to Indirectly Target Extracellular Matrix Components

In addition to directly targeting or exploiting ECM components, other approaches also focus on targeting the upstream or downstream cellular response of the altered ECM in tumors.

Collagen, the most abundant component of ECM, is mainly secreted by fibroblasts (Pankova et al., 2016). The treatment of collagen in the current study is mainly to target the function of cancer-associated fibroblasts (CAFs) (Liu T. et al., 2019). Fibroblast depletion has primarily focused on the targeting of fibroblast populations with positive fibroblast activation protein (FAP), that improves tumor-associated ECM in lung cancer and pancreatic cancer models (Lo et al., 2015). In murine melanoma model, ablation of FAP-expressing CAFs induced a reduction in immunosuppressive myeloid cells (Zhang and Ertl, 2016). However, a phase II trial of FAP inhibition using the small molecule inhibitor Talabostat failed to demonstrate clinical efficacy for colorectal cancer (Narra et al., 2007). It's should be noted that targeting CAFs may cause the progression of cancer in the setting of pancreatic adenocarcinoma (Ozdemir et al., 2015). The depletion of α-smooth muscle actin (α-SMA)-positive myofibroblasts reveals the potential for the dissemination and metastasis of diseases (Ding et al., 2014), which emphasizes the importance of understanding the heterogeneity of fibroblasts both within and between cancer subtypes, and is necessary before the targeting of fibroblasts in human tumors. It's single cell sequencing that probably holds the key to this understanding and enables to identify fibroblast subsets linked to abnormal tumor immunity (Kieffer et al., 2020).

In addition to the depletion of CAFs, other approaches focus on targeting the downstream cellular response to influence ECM. Up to date, the hot targets are the major matrix binding proteins, the integrins and their downstream signaling mechanisms. The use of small molecule kinase inhibitors targeting signaling pathways regulated by ECM such as focal adhesion kinase (FAK) (Jiang et al., 2016) and Rho-associated protein kinase (ROCK) (Johan and Samuel, 2019) has been proved to be effective in targeting the ECM accompanying desmoplasia in cancer.

Based on these preclinical data, several clinical studies have been launched (**Table 1**). According to https://clinicaltrials.gov/, some clinical studies on targeted ECM have been withdrawn or terminated due to various reasons. However, with the deepening understanding of ECM, people are exploring strategies of transforming the ECM into a strong anti-tumor immunity, and preclinical study and clinical research will continue.

CONCLUSION

Growing evidence suggests that tumor immunity and the response to immunotherapy are affected by many factors besides the antigenicity and/or mutational burden of cancer. This wide array of parameters includes the competency of the host immune system and the composition of the tumor-associated ECM.

A great number of studies on the regulation of ECM in cancer immunity are emerging, but there are still some puzzles. For example, what are the differences in ECM remodeling between immune cold tumors and immune hot tumors? What are the differences in the ECM components between those two populations? So far, we have not yet found more detailed and direct updated literature in this field. However, based on the studies of the effect of ECM on the proliferation and infiltration of T cells, we would propose that collagens and PGs will be the main different components of ECM between "cold" and "hot" tumors. Next, we may conduct a study to compare the differences of ECM between these two populations.

Our review has summarized that the components of ECM play a critical role in regulating each step of the cancer-immunity cycle, which also highlights the potential of targeting tumor-associated ECM to improve cancer immunotherapy. According to the common compositional alterations of ECM (collagen and Hyaluronan) and data from some published studies, PEGPH20, targeting Hyaluronan, and Cetuximab targeting collagen may have the potentiality to be explored, although targeting ECM has not yet yielded satisfactory results as an adjuvant immunotherapy. It is important to note that the compositional and structural complexity of the ECM as well as significant intra-tumoral heterogeneity are still yet to be fully understood, which may limit the targeting of ECM. Fortunately, technological advances such as multiplexed-immunohistochemistry, tissue decellularization techniques, single cell sequencing and mass-spectrometry are beginning to address these issues above. In the future, strategies to manipulate the tumor-associated ECM are expected to produce novel approaches to optimize the therapeutic strategies of novel immunotherapies and prolong the overall survival of cancer.

AUTHOR CONTRIBUTIONS

YH, TL, and SD analyzed the data and wrote the manuscript. ZX provided helpful discussion. LW and FL reviewed the manuscript. All authors reviewed the manuscript.

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