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Review Article

The Diverse Roles of the Tumour Microenvironment in Carcinogenesis

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Abstract

Cancer progression heavily relies on the tumor microenvironment (TME), and therapeutic targeting of its components could aid in cancer management. This narrative review highlights the different parts of TME and charts potential targets for cancer therapy. Overall, the influence of the various components of the microenvironment is that of tumor support through immunosuppression, particularly as cancer progresses beyond initiation. Targeting the supporting elements of the TME for therapeutic benefit is possible after a detailed evaluation of the cancer type and stage. Several therapeutic modalities are already well established, and more preclinical and clinical studies are underway.

Keywords: Carcinogenesis, Extracellular matrix, Stromal cells, Tumor microenvironment.

الأدوار المتنوعة للبيئة الميكروية للورم في عملية التسرطن

الخلاصة

تلعب البيئة المحيطة بالورم السرطاني دوراً محورياً في تطور السرطان، ويمكن استهداف مكونات هذه البيئة علاجياً في السيطرة على نمو وانتشار الورم. تسلط هذه المراجعة السردية الضوء على الأجزاء المختلفة للبيئة المحيطة بالورم وتوضح الأهداف المحتملة لعلاج السرطان. بشكل عام، يكون تاثير المكونات المختلفة للبيئة المحيطة بالورم على شكل دعم للورم من خلال تثبيط المناعة، وخاصة مع تقدم السرطان إلى ما بعد مرحلة نشوئه. من الممكن استهداف العناصر الداعمة للبيئة السرطانية لتحقيق فائدة علاجية بعد تقييم مفصل لنوع السرطان ومرحلته، وقد تم بالفعل ترسيخ العديد من الوسائل العلاجية، وهناك المزيد من الدراسات السريرية وما قبل السريرية جارية في الوقت الحالي.

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INTRODUCTION

The tumor microenvironment (TME) is a complex and heterogeneous assembly of tumor cells, infiltrating cells, secreted molecules, and extracellular matrix in which a cancer develops [1-3]. The concept of the TME is embodied by the realization that cancer cells, despite their mutational load, do not act alone in manifesting the disease but are required to recruit and corrupt normal resident cell types [4]. The TME is continually changing in response to signals from tumor cells as well as the evolving environmental conditions. These dynamic processes help cancer cells create their niche that is best suited for the neoplastic progression, gradually modulating it from a niche that attacks cancer to a niche supportive of cancer growth [5,6]. A hallmark of the TME is the presence of immune cells, stromal cells (a heterogeneous collection of connective tissue cells that build organs), blood vessels, and extracellular matrix (ECM) [1,7]. It is now recognized that cancers are also diverse by the nature of their microenvironmental composition and stromal cell proportions or activation states [4,5,8]. The interactions between cancer cells within the TME and the associated immune and stromal cells powerfully influence disease initiation, progression, metastasis, patient prognosis, and the resistance of most cancers towards therapy [4,9]. Early in the development of cancer, a dynamic and reciprocal relationship is established between cancer cells and cellular components of the TME. To overcome hypoxic and acidic conditions, the TME coordinates a program that promotes angiogenesis to provide oxygen and nutrients and remove metabolic waste [1]. This leads the TME to become infiltrated with diverse immune cell types that can carry out both pro- and anti-tumorigenic functions, i.e., tumor-supporting and tumor-suppressive functions, respectively. These immune cells' abilities are influenced by the cancer type in addition to their developmental stage and priming within the tumor mass and at the systemic level. The TME heterogeneity and its continuous change not only promote the progression

of malignancy but are also responsible for resistance towards therapies [10,11].

METHODS

The subject of the tumor microenvironment (TME) and how it affects cancer progression has gained considerable interest in the literature. For this narrative review, literature searches were confined to the years between April 2004 and April 2024. Peer-reviewed articles during this period were examined employing the key phrases given above and the search engines PubMed, Google Scholar, ResearchGate, and Web of Science. The initial collections of publications were screened by the author, taking into consideration the citations of the manuscript and the impact factor of the journal. Those studies that were deemed to fall outside the scope of this basic review were excluded. Moreover, publications before April 2004 were only considered if the content of the article suggested that they represented a significant and/or historic contribution to the review topic.

Components and Interactions of TME

The dynamic nature and type as well as the stage of cancer usually dictate the composition of the TME [12,13]. The TME is, principally, made up of cellular and acellular parts. The cellular part comprises the cancer cells, immune cells, and a plethora of other supporting cells, while the acellular part represents secreted molecules that partly form the extracellular matrix (ECM), acting as a scaffold for other components. A schematic diagram of the general features of a TME is illustrated in Figure 1.

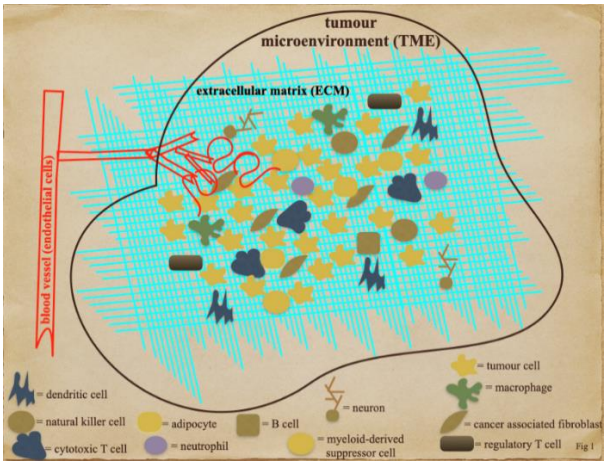

Figure 1: A schematic representation of the components of tumour microenvironment (TME). The TME will also have lymphatic vessels and other cells not represented in the diagram.

Interactions between the cellular constituents and the secreted molecules create a TME that influences cancer development and progression [4,13,14]. For simplicity, the cellular components of the TME are broadly categorized into: 1) tumor cells; 2) immune cells, which can be those that mainly function in the adaptive, innate, or mixed responses of the immune system; and 3) other cells. Tumor cells, themselves, need no introduction in this review, and we will be focusing largely on the roles of supporting cells (Figure 2).

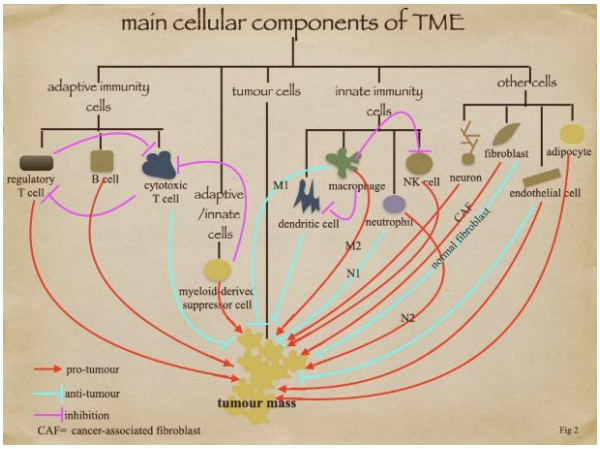

Figure 2: The main cellular components of tumour microenvironment (TME) and a depiction of some of the complex interactions influencing tumour cells. CAF: cancer-associated fibroblast.

Immune cells

The immune cells are a critical part of a TME and can either suppress tumor growth (creating an immune-supportive microenvironment) or promote tumor growth (creating an immune-suppressive microenvironment), depending on the context and cancer type [1]. The immune cells are broadly categorized into the functions they fulfill in the immune defenses, such as adaptive immune cells, innate immune cells, and those with mixed functions of both arms, such as myeloid-derived suppressor cells (MDSCs). The adaptive immune cells, which include T cells and B cells, use their immunological memory to assess and react to threats. The innate immune cells, which include macrophages, neutrophils, natural killer (NK) cells, and dendritic cells (DCs), perform a non-specific but quick response within hours, functioning as a defense mechanism against foreign antigens entering the body.

Other "non-immune" cells in the TME

TME also recruits a multitude of other "non-immune" cells from endogenous tissues to promote its construction. These cells, which can vary significantly between cancer types, include endothelial cells, fibroblasts, adipocytes, and neurons. They are capable of releasing factors that influence various stages of cancer development and progression. Endothelial cells participate in the formation of new blood vessels, which are essential to deliver oxygen and nutrients and remove waste products from the TME [15]. Fibroblasts, referred to as cancer-associated fibroblasts (CAFs) when in the TME, play a role in facilitating crosstalk between cancer cells and other cellular components of the TME. CAFs are often derived from tissue-resident fibroblasts but can

originate from cells such as endothelial cells, adipocytes, and other cells [16]. Adipocytes represent another specialized group of abundant cells in the TME that regulate energy balance and are responsible for storing excess fat. They affect the TME by releasing different substances, such as metabolites, enzymes, hormones, growth factors, and cytokines, which help the tumor grow within the TME [17]. Their main pro-tumor function is realized by the secretion of molecules such as leptin and hepatocyte growth factor causing inflammation and an increase in the likelihood of metastasis. Adipocytes are critical components of breast tissue, as the latter is composed of white fatty tissue. Cells within the TME of breast cancer can stimulate adipocytes to undergo lipolysis to produce free fatty acids to support the growing cancer cells.

The extracellular matrix (ECM)

The extracellular matrix (ECM) is the non-cellular component of the tumour microenvironment (TME). It is composed of a network of macromolecules, including collagens, glycoproteins, hyaluronic acid, laminins, and enzymes, which support biochemical activities and influence functions such as adhesion, communication, and proliferation [8,18,19]. The extracellular matrix provides the scaffolding for the cellular components of the TME and promotes cancer cell dissemination. Solid tumors can contain a large ECM component that constitutes up to 60% of tumor mass, with CAFs being its predominant source [1]. The extracellular matrix acts as a depot for several cytokines and growth factors and plays an important role in creating an immunosuppressive environment conducive to cancer progression [20]. High ECM rigidity enables cancers to be more aggressive, as has been observed in triple-negative breast cancers, which are associated with poor prognostic outcomes [21].

The Influence of TME on Cancer Cells

The impact of the TME's main immune cells on cancer cells is schematically illustrated in Figure 3. The influence of the immune cells on carcinogenesis is largely determined by the nature and levels of secreted factors as well as the stage of tumor progression they encounter during their development and recruitment to the TME. This overall influence polarizes the immune cells into tumor-supportive (pro-tumor) or tumor-suppressive (anti-tumor) cells, as shown in Figure 3. When macrophages are activated, the M1 and M2 subtypes become polarized. The right transcription factors enter the nucleus to aid in the expression of differentiation genes. Once activated and polarized, The M1 macrophages are mainly involved in pro-inflammatory responses exerting anti-tumor influences, and the M2 macrophages are primarily involved in anti-inflammatory responses and pro-tumor influences [22]. The TME contains two main subtypes of neutrophils, N1 and N2, which reflect their anti-tumor or pro-tumor states, respectively [23,24].

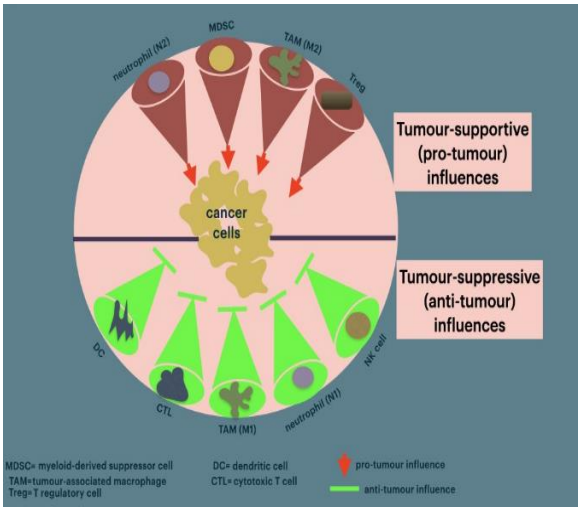

Figure 3: The overall influence of the main immune cells on carcinogenesis in the tumour microenvironment (TME). CTL: cytotoxic T cell; DC: dendritic cell; MDSC: myeloid-derived suppressor cell; TAM; tumor-associated macrophage; Treg: T regulated cell.

Numerous factors within the TME influence the release of neutrophils from the bone marrow and their differentiation into N1 and N2 subtypes, and researchers continue to study these mechanisms [24,25]. Cytotoxic T cells, NK cells, and dendritic cells primarily orchestrate other anti-tumor influences in the TME, as illustrated in Figure 3. Cytotoxic T lymphocytes (CTLs) are the main type of lymphocytes that attack and kill cancer cells based on how they present antigens. They are the immune system's main defense against tumors [26]. We currently define natural killer (NK) cells as effector cells similar to CTLs, which also exert their cytotoxicity against cancer cells. In addition to their cytotoxicity, NK cells have been shown to produce many cytokines, mainly IFN-γ, to modulate adaptive immune responses [27]. Dendritic cells (DCs) are central components of the TME that promote anti-tumor responses. However, the immunosuppressive TME can affect the function of DCs, altering their phenotypes and promoting tolerogenicity [28]. Figure 3 illustrates the effects of myeloid-derived suppressor cells and T regulatory cells on the remaining pro-tumor cells. Myeloid-derived suppressor cells (MDSCs) work to weaken the immune system in the TME by stopping T cells from doing their job and helping cancer cells get away [29]. Regulatory T cells (Tregs) impede monitoring of the immune system and diminish the anti-tumor response in cancer patients [30]. In addition, Tregs support cancer cell survival by releasing growth factors and interacting with stromal cells [1]. Other "non-immune" cells residing in the TME can also have a significant influence on carcinogenesis. The role of endothelial cells in the TME is multifaceted and not only crucial in promoting angiogenesis but also as mediators

in the regulation of the immune response [15]. Endothelial cells play a crucial role in the development of tertiary lymphoid structures and are also associated with the priming, activation, and proliferation of T cells. They do this by presenting antigens to T cells. Normal fibroblasts can exhibit suppressive (anti-tumor) functions through cytokine signaling and the ECM's integrity. It is possible for cancer cells to change normal fibroblasts into cancer-associated fibroblasts (CAFs). This causes a number of pro-tumor signals and the release of enzymes that change the extracellular matrix (ECM). These enzymes change the environment in a way that helps the tumor grow, giving fibroblasts in TME both pro-tumor and anti-tumor roles [31]. Fatty (adipose) tissues make up about 6% of the body mass of fit athletic men and over 30% of obese men, and interactions between fat cells and cancer cells can alter the function of both types of cells and actively alter the TME [17]. When normal adipocytes display an altered phenotype and certain biological features, they become cancer-associated adipocytes (CAAs). In cancers like breast cancer, where adipocytes are close to the cancer cells, the cancer seems to grow and spread. This suggests that fat cells play a role in inflammation and tumor growth [32].

Targeting Components of TME

The tumor microenvironment (TME) is complicated and diverse in its constituents, particularly as cancer progresses in solid tumors. The acquisition of mutations and the development of malignancy often lead to hypoxic conditions and the consequent metabolic remodeling of the TME [33]. The subsequent interactions between cancer cells and other cellular components of the TME, including immune and non-immune cells, result in further modifications to the TME, the development of disorganized vascularization, and the potential for metastasis [34]. This dynamic and continuously changing environment around cancer cells can affect the overall tumor growth and spread [33]. Common treatment modalities include chemotherapy, radiotherapy, surgery, and more recently, therapies that target defined mutations (vulnerabilities) in cancer cells. The literature is abounding with information on these approaches for the avid reader. The current review will exclusively concentrate on cancer treatments that involve the TME and its components, such as immunotherapies, treatments that target endothelial cells and angiogenesis, treatments that target macrophages, treatments that target the extracellular matrix, and other related treatments.

Immunotherapies

Immune cells within the TME are often the target of cancer therapies and can be conveniently dealt with under their types. Examples schematically illustrating the targeting of the major immune cells in the TME are shown in Figure 4.

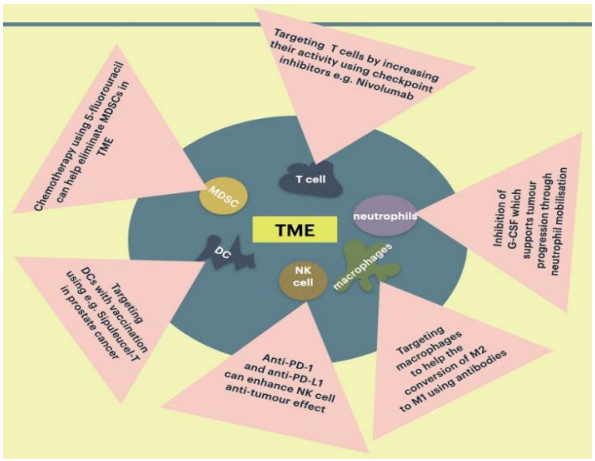

Figure 4: Examples of targeting the major immune cells in the tumour microenvironment (TME). TME: tumor microenvironment; DC: Dendritic cell; G-CSF: granulocyte-stimulating factor; MDSC: Myeloid-derived suppressor cell; NK: natural killer; PD-1 and PD-L1: programmed death receptor and ligand.

T cell-based immunotherapies

T cells are an essential part of the TME, and activating them to eliminate malignant cells constitutes an important pillar in immunotherapy. Through PD-L1/PD-1 (programmed death ligand 1 and its receptor), for example, cancer cells send T cells negative regulatory signals that stop T cells from attacking them. This helps the cancer cells stay alive. These immunosuppressant proteins are normally there to control hyper-immune activity and prevent autoimmunity. T cells highly express PD-1, an immunosuppressive receptor, while cancer cells highly express PD-L1, its main ligand [35]. Because of this, blocking the activity of the PD-L1/PD-1 axis with antibodies, which are called immune checkpoint inhibitors, can restore anti-tumor activity and has become one of the most effective ways to treat cancer [3]. The currently licensed PD-1 inhibitors include Nivolumab, Pembrolizumab, and Cemiplimab, while the licensed PD-L1 inhibitors include Atezolizumab, Durvalumab, and Avelumab. Another major checkpoint protein is CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), which binds to members of the B7 family of proteins on the surface of antigen-presenting cells, thus inhibiting T cell activity [36]. The binding of antibodies, e.g., Ipilimumab and Tremelimumab, can restore the function of T cells. VISTA (V-domain Ig suppressor of T cell activation), TIM3 (T cell immunoglobulin and mucin domain 3), TIGIT (T cell immunoreceptor with immunoglobulin and ITIM domain), and LAG3 (lymphocyte activation gene 3) have all been studied in recent years [3,37]. LAG3 ligands include HLA-II (human leukocyte antigen class II) and LSECtin (liver sinusoidal endothelial cell lectin). More than ten blocking agents, such as Relatlimab and Ieramilimab [37,38], are in clinical trials. Galectin-9 is a TIM-3 ligand, and the antibody Sabatolimab seems to be able to block both TIM-3 and PD-1 while also making T cells

better at fighting tumors [39]. TIGIT binds to the CD155 ligand, which is overexpressed on cancer cells. There are several monoclonal antibodies (mAbs) available for TIGIT, and Tiragolumab, either as a monotherapy or in combination with Atezolizumab (an anti-PD-L1 antibody), has been shown to improve the overall response in metastatic non-small cell lung cancer (NSCLC) [40]. VISTA expressed on T cells acts as a receptor that interacts with ligands, such as VSIG-3 (V-set immunoglobulin domain containing 3) and PSGL-1 (P-selectin glycoprotein ligand 1), inhibiting T cell activity. Several small-molecule inhibitors, such as CA-170, and blocking antibodies, such as VSTB11, are in various stages of clinical trials [41]. Apart from the use of immune checkpoint blockers to target the TME in cancer, other T-cell-based therapeutic strategies have been investigated. These include adoptive cell therapy using autologous or allogeneic T cells and CAR-T cells (where CAR stands for chimeric antigen receptor), and details of these treatment modalities can be found elsewhere [42–44]. Moreover, a similar cancer treatment using CAR-NK cells instead of CAR-T cells has also been studied and concluded to be effective and safer than CAR-T therapy, as these cells rarely cause graft-versus-host disease (GVHD), cytokine release syndrome (CRS), and neurotoxicity [45,46]. Targeting Tregs in the TME was also considered a strategy for the treatment of cancer. Tregs in the TME can be classified into three main types according to the level of the expression of two proteins, FoxP3 (F) and CD45RA (C). These types are non-Tregs (with low F and no C), naive-Tregs (with low F and positive C), and effector-Tregs (with high F and no C) [47]. Non-Tregs have no inhibitory effects; naive-Tregs are weakly suppressive, while effector-Tregs possess the strongest suppressive activity. However, reducing Tregs in the TME may also lower Tregs systemically and hence increase the risk of immune-related adverse effects necessitating careful selective depletion of Tregs subtypes.

B cell-based immunotherapies

B cells participate in the humoral immune response by generating antibodies and cytokines, but they also play a role in antigen presentation and immunological control. In the setting of the TME, B lymphocytes are primarily concentrated around the tumor margin and nearby lymph nodes. Tumor-infiltrated B cells can develop and gain a regulatory function, resulting in Bregs that can promote tumor growth by inhibiting anti-tumor immune responses [48]. The administration of PD-1 antibodies (such as Nivolumab or Pidilizumab) has been found to reverse B cell-mediated immunosuppression [49].

Targeting dendritic cells (DCs)

Dendritic cells (DCs) are the professional antigen-presenting cells that capture antigens released by the tumor and present them to T cells in the lymph nodes to generate tumor-specific cytotoxic T cells [50]. They can also stimulate NK cells and B cells to activate their parts of the immune response [50,51]. Targeting and activating DCs with vaccination has been successful in the treatment of prostate cancer using the widely licensed product Sipuleucel-T (Provenge) [1,52].

Targeting macrophages

Tumour-associated macrophages (TAMs) are one of the most important components of TME and, as such, represent a potential target for cancer therapy. At present, the most studied approach to manipulating TAMs is their reprogramming from being pro-tumor (M2) to anti-tumor (M1) cells. M1 cells have an inhibitory influence on tumor cell survival and possess anti-angiogenic effects, while M2 cells can promote metastasis, inhibit anti-tumor activity mediated by T cells, and promote tumor progression and angiogenesis [53, 54]. As the tumor progresses, the M2 subtype will dominate the TME. The conversion of M2 to M1 macrophages is mostly achieved using antibodies to target colony-stimulating factor 1 (CSF1) and its receptor (CSF1R), several toll-like receptors, and histone deacetylase (HDAC) [55–57]. Other strategies include using CAR-M based on studies illustrating that it can transform M2 into M1 [58].

Targeting neutrophils

Targeting neutrophils in the TME can also be a strategy for anti-cancer therapies. Neutrophils, in the context of TME, can be either the anti-tumor (N1) type or the pro-tumor (N2) type [59]. The N1 subtype directly kills tumors by releasing reactive oxygen species (ROS) and reactive nitrogen species (RNS), while the N2 subtype inhibits the function of NK cells, recruits M2 and Tregs, and secretes the metalloproteinase 9 (MMP9) enzyme to promote angiogenesis and metastasis [60]. Treatment strategies can include suppressing the N2 subtype by altering their recruitment and migration and/or increasing the anti-tumor N1 subtype. The cytokine granulocyte colony-stimulating factor (G-CSF) can support tumor progression by mobilizing neutrophils and neutralizing them or inhibiting IL-17, its upstream regulator, which can prevent neutrophil accumulation [61,62]. On the other hand, the anti-tumor ability of neutrophils can be improved by targeting Fc receptors through antigen-dependent cytotoxicity. Altering neutrophil polarization is also a possible therapeutic strategy through which the immunosuppressive cytokine, TGF-β, can differentiate neutrophils into the N2 phenotype, and blocking this cytokine using an inhibitor such as SM16 can result in the accumulation of the N1 subtype [63].

Targeting natural killer (NK) cells

Natural killer (NK) cells are responsible for destroying tumor cells and preventing tumor initiation and

progression. Their direct cytotoxicity stems from death receptor signaling, perforin, and granzymes [27]. However, tumor cells can escape NK cell destruction by binding to inhibitory receptors expressed on the surface of NK cells. Moreover, the production of TGF-β and other anti-inflammatory cytokines in the TME can inhibit NK cell activation [64,65]. Anti-PD-1 and anti-PD-L1 can enhance NK cell-mediated anti-tumor effects. The interaction of PD-1 expressed in NK cells with PD-L1 expressed in cancer cells can decrease the responses of NK cells, and blocking these proteins can increase NK immune responses and cytotoxicity in mouse tumor models [66,67].

Targeting myeloid-derived suppressor cells (MDSCs)

These are diverse cell groups that originate from the bone marrow lineage and exhibit immunosuppressive characteristics [68]. Certain chemotherapy drugs, targeted drugs, all-trans retinoic acid, and agents that block chemokine receptors like CCR5 on MDSCs can effectively remove these cells from the TME and restore anti-tumor immunity to the microenvironment [69–71]. The chemotherapy drug 5-fluorouracil can help eliminate the MDSCs in the TME [72]. The targeted drug, Apatinib, and the all-trans retinoic acid can downregulate the proportion of MDSCs and reduce their number in blood circulation [73,74]. Treatments to inhibit the immunosuppressive function of MDSCs can also be of benefit in reducing their influence in the TME, thus aiding cancer treatment. Such inhibitors can include phosphodiesterase 5 inhibitors such as Sildenafil and Tadalafil [75,76]. Celecoxib, an immunomodulator targeting the COX-2 enzyme, can also suppress the activity of MDSCs [77]. In animal models of tumors, using immune checkpoint inhibitors along with monotherapies that target MDSCs makes the effects stronger [68]. Additionally, the use of multiple anti-MDSC modalities could be a promising strategy. Table 1 and Table 2, respectively, provide a brief outline of the targeting of immune cells and immune cell-associated molecules in the TME.

Table 1: Targeting the immune cell components of the tumour microenvironment

Manipulated target cells	Intervention	Brief description of intervention	Reference
T cells	TIL-ACT	Lymphocytes isolated from patient's tumour and returned after activation and expansion *in vitro*	[78]
	CIK-ACT	PBMCs treated with IFN-γ, IL-2 and anti-CD3 antibodies to differentiate into NK-T cells	[79]
	CAR-T	Lymphocytes isolated from blood then genetically modified and expanded *in vitro* before administration	[79]
	Treg	Antibodies and small molecules targeting highly expressed proteins in Tregs	[80]
B cells	PD-1 antibodies	Nivolumab and Pidilizumab reversing immunosuppression	[49]
Dendritic cells	As vaccines	Through the capture of antigens and presentation to CTLs	[50]
Neutrophils	Neutralising G-CSF	Inhibiting the effect of G-CSF in mobilizing neutrophils and cancer progression	[62]
Natural killer cells	PD-L1/PD-1	Blocking PD-L1/PD-1 axis can increase NK cell responses	[66]
Myeloid-derived suppressor cells	Phosphodiesterase-5 inhibition	Tadalafil to inhibit immunosuppressive function of MDSCs	[76]
Macrophages	Engineering chimeric antigen receptor macrophages (CAR-M)	CAR-M demonstrated phagocytosis *in vitro* and decreased tumour burden in mouse models	[58,81]

TIL-ACT: tumour-infiltrated leukocytes adoptive cell therapy, CIK-ACT: cytokine-induced killer adoptive cell therapy, PBMCs: peripheral blood mononuclear cells, IFN-γ: interferon gamma, IL: interleukin, CD: cluster of differentiation, NK-natural killer, CAR-T: chimeric antigen receptor T cell, Treg: regulatory T cell, PD-1: programmed death 1, PD-L1: programmed death ligand 1, G-CSF: granulocyte colony-stimulating factor, CTLs: cytotoxic T lymphocytes, MDSC: myeloid-derived suppressor cell.

Table 2: Targeting molecules of the immune system in the tumour microenvironment

Manipulated target molecules	Intervention	Brief description of intervention	Reference
PD-L1 (ligand)	Inhibition	Using Atezolizumab, Durvalumab and Avelumab	[82,83]
PD-1 (receptor)	Inhibition	Using Nivolumab, Pembrolizumab and Cemiplimab	[82,83]
CTLA-4	Inhibition	Using Ipilimumab and anti-CTLA-4 nanobody	[84,85]
LAG-3	Inhibition	Using Relatlimab	[86]
TIM-3	Inhibition	Using Sym023 antibody	[87]
TIGIT	Inhibition	Using Vibostolimab and Tiragolumab	[88]
VISTA	Inhibition	Using PH-sensitive antibody SNS-101	[89]

PD-1: Programmed death 1, PD-L1: programmed death ligand 1, CTLA-4: cytotoxic T lymphocyte-associated protein 4, LAG-3: lymphocyte activation gene 3, TIM-3: T cell immunoglobulin and mucin domain-3, TIGIT: T-cell immunoreceptor with immunoglobulin, and ITIM domain, VISTA: V-domain immunoglobulin (Ig) suppressor of T-cell activation.

Targeting endothelial cells and angiogenesis

The TME needs to be able to have its supply of blood vessels, as the vasculature not only provides oxygen and nutrients and removes waste products but also provides channels for metastasis [90]. Blood vessels are mainly constructed of endothelial cells, and targeting these cells and their cytokines is a further strategy to counteract cancer progression. Several anti-angiogenic drugs have been developed to target endothelial cells, which can be put into three main groups: a) monoclonal antibodies (mAbs), b) tyrosine kinase inhibitors, and c) inhibitors of endogenous angiogenesis. The monoclonal

antibodies, such as Bevacizumab and Ramucirumab, mainly bind to VEGF, and the tyrosine kinase inhibitors, such as Sorafenib and Sunitinib, mainly bind and inhibit VEGFR and PDGFR. The endogenous angiogenesis inhibitors, such as Endostar, mainly exert their effects by downregulating the expression of VEGF and its receptors.

Targeting cancer–associated fibroblasts (CAFs)

Fibroblasts are one of the most abundant and functional cell types in the TME, accounting for 70–90% of tumor volume in breast and pancreatic malignancies [91]. Fibroblasts are distinguished by their elongated shape and are abundant in connective tissues in a latent condition [54]. When stimulated by inflammatory mediators like TGF-β and LPA, cells create cytokines that govern communication with other cells, including immune cells [92]. Cancer-associated fibroblasts (CAFs) are activated fibroblasts that live in the tumor microenvironment. Cancer-associated fibroblasts promote carcinogenesis in a variety of ways, including cytokine release, altering the ECM, supplying metabolites to cancer cells, boosting angiogenesis, and inhibiting anti-tumor immune cells [93]. CAFs contribute significantly to the creation and turnover of the ECM by producing structural molecules such as collagen, fibronectin, and laminin, as well as releasing enzymes that modify and degrade these structures, such as lysyl hydroxylases and metalloproteinases [94]. The direct technique for eliminating CAFs from the TME is primarily dependent on the presence of surface indicators such as fibroblast activating protein (FAP). This protein is not found in normal tissues, but rather in activated CAFs in the TME. Vaccines based on FAP can decrease breast cancer growth by eliciting FAP-specific CTL responses [95]. In addition to directly targeting CAFs to impact their quantity and activity, some treatments can indirectly affect CAFs, such as the administration of Scriptaid, a small-molecule HDAC inhibitor that inhibits CAF differentiation and reduces CAF number [96].

Targeting the adipocytes in the TME

The fat cells (adipocytes) are inert; however, those residing in the TME are activated by cancer cells to yield cancer-associated adipocytes (CAAs). CAAs can promote tumorigenesis through the secretion of adipokines, inflammatory factors, and the production of fatty acids [97]. CAAs are important components of the TME of cancers of the breast, ovary, prostate, kidney, colon, and stomach [98]. Transforming CAAs into normal adipocytes and inhibiting related bioactive molecules are effective methods for treating tumors. For example, metformin can exert anti-tumor effects by regulating adipocytes' leptin and normalizing dysfunctional adipocytes [99]. In recent years, metformin has been found to have a significant inhibitory effect on the growth and differentiation of human adipose cells [100]. In addition, therapies targeting bioactive molecules secreted by CAAs can also inhibit tumors, such as the use of peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, e.g., rosiglitazone and pioglitazone [101]. The targeting of the "non-immune cell" components of the TME is summarized in Table 3.

Table 3: Targeting the "non-immune' cell components of the tumour microenvironment

Manipulated target cells	Intervention	Brief description of intervention	Reference
Endothelial cells and vasculature	Targeting VEGF	Using antibodies against Bevacizumab and Ramucirumab	[102]
Fibroblasts and cancer-associated fibroblasts	Targeting FAP surface marker	Whole cell vaccine expressing FAP reduced tumour growth and improved survival	[103]
Adipocytes and cancer-associated adipocytes	Using Metformin	Reducing the tumour-promoting effects of adipocytes	[99,100]

VEGF: vascular endothelial growth factor, FAP: fibroblast activation protein.

Targeting the extracellular matrix (ECM)

The ECM plays multiple roles in tumorigenesis. It provides mechanical support for the cellular components, modulates the TME, and acts as a reservoir for signaling molecules. Interactions between cancer cells and the TME often result in stiffness in the ECM, leading to signaling disturbances and further malignant transformations. The following components of the ECM can be targeted for therapeutic benefit in cancer: 1) collagen, 2) TGF-β, 3) TGF-βR, 4) AT1R, 5) fibronectin, and 6) sensors for matrix stiffness. Collagen is a fundamental component of the ECM, and its dysfunction could facilitate the penetration of many chemotherapeutic drugs and nanoparticles. Because TGF-β is so important for making collagen, signaling pathways that involve it are the best place to start if you want to stop collagen from being made [104]. However, targeting TGF-β should be regarded with caution due to the prominent role of this molecule in inflammation and tumorigenesis [105]. Initial trials have found that the blood pressure drug Losartan can contribute to the inhibition of collagen synthesis [106,107]. Collagenases, which are enzymes, have the ability to degrade collagen and reduce the stiffness of the extracellular matrix (ECM), thereby enhancing the efficiency of drug delivery [108]. However, the use of these enzymes raises concerns as their degradation releases cytokines and growth factors embedded in the ECM, thereby promoting cancer progression. Additionally, the breakdown of collagen may facilitate tumor metastasis [109]. The use of "anti-collagen" treatments should be carefully considered and ideally should be used for cancers detected early and that have

shown no signs of metastasis. The signaling molecule TGF-β plays a dual role in cancer, acting as a tumor suppressor during the initial stages but functioning as a driver of tumors in advanced stages [110]. When TGF-β binds to TGF-βR, the transmitted signal leads to a pro-apoptotic effect [91]. Therefore, TGF-βR is downregulated or mutated in various types of cancers. However, cancer cells themselves overexpress TGF-β-promoting fibroblasts to make ECM components and enhance the differentiation and function of Tregs to induce immunosuppressive TME [111]. Small molecules have been used to target TGF-βR, such as SB-431542 and SB-505124, and have been shown to suppress proliferation, motility, and vascularization in mouse models of glioma and renal carcinoma [112-114]. The leading receptor for angiotensin II to exert vasoconstriction is the Angiotensin II type 1 receptor (AT1R). AT1R plays an important role in promoting cell proliferation, angiogenesis, and inflammation in the TME. This receptor activates EGFR, thus promoting tumorigenesis and increasing the expression of VEGF, which contributes to angiogenesis [115]. Moreover, AT1R promotes the transcription of cytokines, resulting in inflammation. The use of angiotensin receptor blockers (ARBs) such as Candesartan was shown recently to suppress the growth and metastasis of cancer [116,117]. Hyaluronic acid (HA) is another important component of the EMC that could be targeted. Two types of therapeutic strategies have been employed in targeting HA: 1) the inhibition of HA synthesis and 2) the enhancement of HA degradation. One compound that has emerged as an inhibitor of HA synthesis is 4-methylumbelliferone (4-MU) and has been found to be beneficial in animal models of ovarian cancer [118]. In terms of improving the breakdown of HA, hyaluronidase has been shown to help lower the number of certain cancers in the TME [108,119]. The extra domain B (EDB) of fibronectin is frequently upregulated in tumor vasculature, and several targeted cancer therapies have been developed for that purpose [91]. For example, the fusion product huBC-1-mIL-12 (which is made up of the cryptic domain next to human EDB fused with murine IL-12) stopped different kinds of cancer from growing in mice [120]. Many trials were conducted to demonstrate targeting the sensors of matrix stiffness through the inhibition of integrin and showed that this approach could strongly suppress cancer progression [121]. For example, Vitaxin (a humanized mAb targeting integrin) yielded therapeutic potential in patients with cancers of the breast, colon, and lung. The discoidin domain receptor (DDR), like integrin, can also sense the stiffness of the TME [91]. DDR1 overexpression has been observed in several cancers and correlates significantly with poor prognosis in certain ones [122,123]. Knocking down DDR1 using siRNA was found to inhibit cell migration in the pancreas [124]. An outline of targeting the essential components of the extracellular matrix in the tumour microenvironment is given in Table 4.

Conclusion

Since the TME was conceived, a multitude of the literature has indicated that without such a microenvironment, an initial cancer cell would not progress to a tumor. The overall influence of the TME, particularly as tumorigenesis progresses, is tumor-supportive. This pro-tumor (immunosuppressive) microenvironment is orchestrated by numerous cross-talks between cellular components of the TME and is driven by cytokines, growth factors, and other molecules. Various approaches have been suggested to manipulate the TME to exert more anti-tumor effects. Some of these therapeutic modalities have gained regulatory approval and are now marketed for their value in fighting cancer. Others are at different stages of preclinical and clinical investigations, holding the promise of a rewarding future for cancer immunotherapies.

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