Tumor microenvironment components: Allies of cancer progression

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ABSTRACT

Cancer is a disease that affects millions of individuals worldwide and has a great impact on public health. Therefore, the study of tumor biology and an understanding of how the components of the tumor micro-environment behave and interact is extremely important for cancer research. Factors expressed by the components of the tumor microenvironment and induce angiogenesis have important roles in the onset and progression of the tumor. These components are represented by the extracellular matrix, fibroblasts, adipocytes, immune cells, and macrophages, besides endothelial cells, which modulate tumor cells and the tumor microenvironment to favor survival and the progression of cancer. The characteristics and function of the main stromal components and their mechanisms of interaction with the tumor cells that contribute to progression, tumor invasion, and tumor spread will be addressed in this review. Furthermore, reviewing these components is expected to indicate their importance as possible prognostic markers and therapeutic targets.

1. Introduction

Cancer is one of the most frequently occurring diseases in the world, and it is estimated that in 2018, about 9.6 million cancer-related deaths occurred, at an annual cost of approximately 1.16 trillion dollars [1]. Cancer is caused by a wide range of genetic and epigenetic alterations that confer unique features to cancer cells that allow them to exhibit autonomous proliferation, resistance to cell death, invasiveness, evasion of the immune system, replicative immortality, and metastatic potential [2]. In addition to the factors related directly to tumor cells, interactions between tumor cells and stromal components of the tumor microenvironment have a major impact on tumor progression, contributing to most of the features of these cells and forming a favorable environment for the development of cancer [3].

Cancers form complex and heterogeneous environments consisting of multiple cells that proliferate, such as cancer cells and stromal cells, and the extracellular matrix (ECM[1]), which directly or indirectly contributes to the maintenance of tumor cells. The stroma of normal tissues acts as a support structure for organs, and this component becomes essential for maintaining the tumor microenvironment in cancer, being responsible for providing nutrients and support to cancer cells [4]. Therefore, determining the contribution of each stromal element in carcinogenesis can assist in diagnosis and cancer therapy [5,6].

Tumor cells, like other cells in the body, require nutritional support, gas exchange, and withdrawal of metabolites for growth. This contribution is provided in part by circulation through blood vessels, which also serve as the entrance and exit of immune cells and other circulating cells from the bone marrow. This great need for nutrition and oxygen by tumor cells causes the occurrence of a high rate of angiogenesis in tumors so that they can maintain constant proliferation [7].

Establishing a functional vascular network is important for growth and tissue homeostasis. The blood vessels are a complex network that depends on the balance of growth factors and various vascular and nonvascular cell components. It is important to consider that these factors lose their balance in cancer, allowing structurally and functionally different tumor vasculature to develop [8].

Tumors are composed of different components in addition to neoplastic cells. The non-cancerous components include cells such as
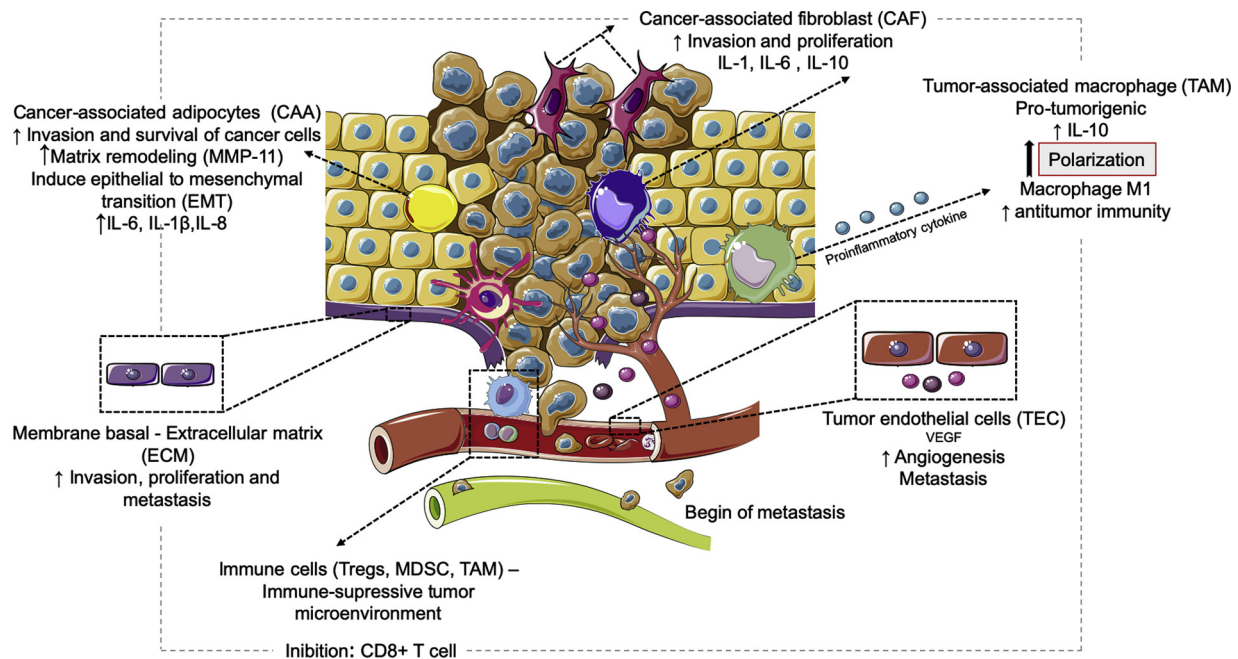
Fig. 1. Simplified Scheme of Tumor Microenvironment Components and their Contribution to Tumor Progression.

Several factors expressed by different tumor microenvironment components that contribute to processes related to tumorigenesis, since they are closely related to the cancer cells. The extracellular matrix facilitates invasion, tumor progression and metastasis through the matrix remodeling and angiogenesis increment. There is also the passage of immune cells to the tumor microenvironment, generating an immunosuppressive environment as well as the output of neoplastic cells into the blood and lymph circulation. Angiogenesis is essential for the development process of new vessels into the tumor, occurs under the influence of pro-angiogenic molecules produced by endothelial cells, and VEGF, which may also be produced by other neoplastic and microenvironmental cells such as macrophages and fibroblasts. Macrophages are the major cell related tumor immunity due to its large amount. At the beginning of tumor process is common the presence of M1 macrophages with antitumor activity. However in more advanced stages have a similar phenotype to M2 macrophages and (Tumor-associated macrophages) TAM called, having pro-tumorigenic activity, especially for high production of IL-10. CAFs (Cancer-associated fibroblasts) may promote tumor growth, invasion and angiogenesis. Cancer-associated adipocytes (CAAs) promoting a chronic inflammatory environment, invasion, and malignant progression with great IL-6 production.

This figure was prepared using a template on the Servier medical art website (http://www.servier.fr/servier-medical-art).

fibroblasts and endothelial cells, as well as immune cells. This set is called the tumor stroma and is a participant in the tumor micro-environment. The microenvironment plays a critical role in many aspects of tumorigenesis, such as generating tumor vasculature, which is highly implicated in the progression to metastasis. More recently, it has become clear that the microenvironment of the tumor also affects the response to therapies. In addition, tumor stroma modulation can improve the effectiveness of existing therapies and present new opportunities for therapeutic targeting [9].

The main components and stromal cells are associated with the cancer cells of the immune system, capillaries and cells of the vascular system, mesenchymal cells of support such as fibroblasts and adipocytes, and the ECM, which surrounds the cancer cells (Fig. 1). Besides cells, the stroma also comprises growth factors, cytokines, chemokines, and antibodies [10]. Thus, the aim of this review is to discuss the stromal components and their factors that assist in angiogenesis, tumor progression, and invasion, given its increasing focus in studies, particularly to understand how these components influence the processes involved in tumor progression, to determine the possibility of being used as factors in diagnosis and prognosis, and to identify possible therapies directed against the microenvironment components.

2. Extracellular matrix in tumor development

The ECM is formed from a network of protein macromolecules, mostly structural proteins, glycoproteins, and proteoglycans [11,12]. Initially, the ECM was described as a stable structure that had only functioned to provide structural support; however, it is presently known that the ECM is highly dynamic and participates in various other cellular processes, such as proliferation, cell migration, and growth. Thus,

the main function of this component is to provide structural support to maintain the tissue architecture and nutritional support to the surrounding cells [13]. The ECM also controls the passage of growth factors and cytokines, favoring intercellular communication. Furthermore, it is responsible for the formation of the basal membrane, together with epithelial, endothelial, and stromal cells [14,15].

In cancer, the ECM is composed of a large variety of components and is recognized as a key component for promoting stromal tumor development by facilitating invasion, progression, and metastasis [16]. In the tumor microenvironment, the ECM is present in an unregulated, disorganized manner in terms of biochemical and physical properties, as well as architectural aspects [14,17]. Thus, ECM reorganization and molecular signals originating from other stromal cells can serve as important targets in the study of tumor biology and oncology therapies [16].

An important component of the ECM is collagen, which is responsible for providing structural support and directing cell migration and chemotaxis. In cancer, there is a greater deposition of collagen and increased activity of matrix metalloproteinases (MMP) and other components, such as proteoglycans. Commonly, the tumor stroma exhibits great rigidity due to the increased activity of lysyl-oxidase, which acts by crosslinking collagen fibers, thereby facilitating the growth and proliferation of cancer cells [17,18]. Furthermore, these collagen fibers have higher linearization in cancer lesions. Another change is related to the dysregulated collagen remodeling process that results in increased collagen degradation by proteases, which can facilitate the invasion of cancer cells through the basal membrane [13].

Physiologically, the ECM makes an important contribution by serving as an essential acellular component of the adult stem cell niche, maintaining the differentiation-related properties of these cells and

Table 1
Therapeutic possibilities directed against components of the tumor microenvironment.

Stromal target	Treatment possibilities	Mechanism of action in the stromal component	Type of cancer	Author / Reference
Cancer-associated fibroblasts (CAFs)	Conophylline	Inhibits activity and proliferation of CAFs	Pancreatic cancer	[88]
	Inhibitors of Fibroblast activation protein (FAP)	Inhibits activation of CAFs	Pancreatic cancer	[89]
Tumor-associated macrophages (TAMs)	Inhibitors of CSF-1 and MDSCs	Reduction in the recruitment of TAMs	Prostate cancer, lung, ovary, pancreas	[90]
	Inhibitors of cytokines produced by TAMs	Decreases macrophage infiltration	Lung cancer	[91]
Extracellular matrix (ECM)	Inhibition of the process of TGFβ	Reduced secretion of collagen I and desmoplasia	Breast tumors	[92]
	Agonists of angiotensin II receptors	Increased patient survival	Gastroesophageal cancer	[93]
	Inhibitors of MMPs (Clinical Assays: Antibody Fab3369 - MMP-14 and JNJ0966 - MMP-9)	Reduction in ECM degradation and consequent lower neoplastic invasion	Of triple-negative breast cancers	[94,95]
Angiogenic components	Inhibitors VEGF/VEGFR2	Inhibition of tyrosine kinase pathways	Advanced Renal cell carcinoma, and soft tissue sarcoma	[96]
			Lung cancer	[97]
	M-TOR inhibitors/AP-1 /VEGF	Indirect decrease in endothelial proliferation	Ovarian Carcinoma	[98]

subsequent cell division [17]. Its function in the stem cell niche is varied and depends on the cell–cell contact, allowing the stem cells to maintain their properties, polarity, and orientation of the mitotic spindle. Thus, asymmetric cell division occurs, which is essential for the self-renewal and differentiation of stem cells. The stem cell differentiation mechanism is highly controlled by homeostasis, and its imbalance can lead to the appearance of tumor-initiating cells, called cancer stem cells [17,19]. Thus, the role that the ECM plays in the stem cell niche is as a facilitator of malignant transformation. The abnormal presence of the ECM in cancer or when cell–cell contact loss occurs leads to increasing expansion of cancer stem cells, which begin to divide symmetrically, with a consequent increase in undifferentiated cells, which are characteristic of the tumor process [19].

New molecules have been increasingly discovered in the ECM that are associated with an increase in tumor angiogenesis, which is supported by the high capacity of these components affecting endothelial cells and promoting the growth of new vessels in the tumor. Thus, degradation of the ECM by proteases or endopeptidases (MMPs) is a fundamental process that enables the migration of vessels toward the angiogenic stimulus through the ECM [20] and enables the release of angiogenic factors retained within [21,22].

Fibrosis also appears to be related to an increased risk of cancer, but the mechanism remains unknown [23]. However, it is known that an ECM with high fibrous rates facilitates the change in polarity in epithelial cells, showing a profile of abundant release of growth factors and promotion of cell proliferation and early cancer progression through different signaling pathways. These facts are confirmed by the high degree of desmoplasia displayed in the tumor stroma [24].

Another example of a molecule that interacts with different components of the ECM and appears to be related to increased angiogenesis is fibronectin. This molecule has been shown to stimulate the survival of endothelial cells and facilitate the connection with these integrins present in the matrix, which is an important process for the formation of new vessels. In addition, components such as laminin, proteoglycans, and hyaluronan also seem to be related to angiogenesis through complex cellular interactive mechanisms [22].

3. Angiogenic molecular basis involved in cancer maintenance

In cancer, the stimulation of pro-angiogenic molecules can be detected in both arising tumor cells and other cells in the tumor microenvironment. Currently, there are numerous recognized signals responsible for firing the angiogenic switch, such as different gene mutations involved in oncogene activation and deletion of tumor suppressor genes, as well as oxidative and mechanical stress and hypoxia [25].

The main molecule responsible for blood vessel morphogenesis is the vascular endothelial growth factor (VEGF), a member of a large family of angiogenic inducers that binds to the transmembrane receptor tyrosine kinase exhibited by endothelial cells. Other important proangiogenic factors are platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), placental growth factor, and angiopoietin-1. The described molecules that inhibit the angiogenic process are, for example, thrombospondin-1 and some other derived proteins, such as statins. In general, the balance of the molecular levels of these activators and inhibitors will determine the quiescent state of endothelial cells [26].

VEGF is a member of a family of growth factors derived from platelets and one of the most studied vessel growth enablers. Its role ranges from chemotaxis and the differentiation of endothelial precursor cells (angioblasts) to the proliferation of endothelial cells and angiogenic remodeling, as well as the maintenance of vascular homeostasis. Various cell types such as endothelial cells, fibroblasts, macrophages, and immune cells can produce and release VEGF, although tumor cells are the main producers [27–29].

PDGF binds to tyrosine kinase-like receptors (PDGF receptors), and

Table 2
Potential prognostic and predictive markers stromal for cancer.

Component stromal evaluated	Possible prognostic markers identified by immunohistochemistry	Contribution to tumor progression	Author/ Reference
Cancer-associated fibroblasts (CAFs)	Positivity for alpha smooth muscle actin (αSMA) and vimentin	Greater contractility of fibroblasts	[102]
	Paladin (actin binding protein)	Expression of genes related to collagen deposition and activation of MMPs	[103]
	Fibroblast activation protein (FAP), fibroblast specific protein-1 (FSP-1) and stromal cell-derived factor 1 (SDF-1)	Collagenase activity, increasing degradation of ECM	[104,105]
	invasiveness and aggressiveness indicators (SL1, TSP-1 and Tn-C)		[106]
Tumor-associated macrophages (TAM)	TAM and intratumoral stromal CD68+ and CD163+	Immunosuppression and angiogenesis	[107]
Extracellular matrix (ECM)	MMP2/MMP9/CXCR4	Migration and invasion through regulation of MMPs	[108]
	Periostin	Cell survival, angiogenesis, invasion, metastasis and epithelial-mesenchymal transition (EMT)	[109]
Angiogenic markers	VEGF, CD31, CD105	Stimulate tumor angiogenesis pathways	[110]

the activation of the PDGF-stimulated angiogenic process occurs via the PI3K/Akt signaling pathway. After ligation, this factor can promote the maturation of neoformed vessels, as it is responsible for the attraction of smooth and pericyte muscle cells [30]. Once in the tumor environment, the recruited pericytes are responsible for stabilizing the tumor vasculature [31]. FGFs, specifically FGF2, are representatives of the tumor stroma and angiogenic inductors. Their function is related to the activation of endothelial cells by specific receptors (FGF receptors) and microenvironment cells. Thus, they have the function of enhancing the angiogenic process for fibroblast activation and subsequent induction of other cells to produce other angiogenic factors using signaling pathways similar to those of VEGF or VEGF indirectly through the release of endothelial and stromal cells [32].

Endothelial cells are responsible for establishing the transport of nutrients and activating molecules between the plasma and tissue, besides secreting angiogenic factors, such as proteins. These factors enable communication between cells to maintain homeostasis and vascular permeability [33]. In cancer, tumor vasculature endothelial cells have different characteristics and are called tumor endothelial cells (TECs). TECs are related to a higher power of cell migration and proliferation, as well as being more responsive to pro-angiogenic factors, such as VEGF, promoting tumor angiogenesis [34].

Endothelial cells respond to stimuli from tumor stromal cells, such as growth factors and cytokines, favoring their change to the phenotype of TECs. These cells are responsible for tumor neovascularization, breaking through the basal membrane, thus degrading the ECM by forming capillaries to invade the ECM and allowing for the survival of tumor cells. This process is aided by pericytes and smooth muscle cells, which are responsible for vascular maturation. Contrary to what occurs in normal vessels, tumor vessels have an abnormal pericyte coverage, indicating that they present structural immaturity [35]. In tumor vessels, there is a dissociation between endothelial cells and pericytes, contributing to abnormal functional properties of new vessels being formed. Decoupled pericytes can migrate to angiogenic stimulus areas, adhering to endothelial cells present in the vessels in formation, promoting the enhancement of proliferation and vascular stabilization [36].

Collagen also has important contributions in tumor angiogenesis, since members of this family are present in the vascular basal membrane. Type I collagen is responsible for promoting the formation of the vascular lumen, being important in the initial process of vascularization [37]. Collagen type IV, a basal membrane constituent, allows for the adhesion and migration of endothelial cells, but cancer shows the same dual function of promoting angiogenic stimuli at the beginning of the process and inhibiting tumors in advanced stages [38].

Tumor metastasis occurs because of the overexpression of angiogenic factors in the tumor microenvironment, which facilitates the exit of tumor cells through blood and lymph vessels [29]. Metastasis occurs in advanced stages of cancer, a process by which tumor cells can form migratory foci and gain dissemination pathways. Alterations in the ECM allow for the detachment and displacement of tumor cells through the cellular interstice. Chemokines, such as chemokine ligand (CCL)19 and CCL21 produced by endothelial cells, are responsible for the chemoattraction of tumor cells toward blood vessels. Once they penetrate the vessel, these cells can gain circulation, survive at this site, and eventually leave and gain new sites of development (pre-metastatic niche), forming new tumors [39].

Tumor angiogenesis is a critical process in tumor progression, since new blood vessels are responsible for the provision of oxygen and nutrients to the tumor cells, allowing for their expansion, as well as enabling the metastatic process and entry of immune cells [40]. TECs, which are morphologically and functionally distinct, are associated with tumor cell progression, which enables tumor survival [34].

4. Fibroblasts in the tumor microenvironment

Fibroblasts are connective tissue cells of mesenchymal origin present in the ECM. They are mostly responsible for its synthesis and participate in processes such as deposition and remodeling of the ECM, regulation of inflammation, and scarring. These cells also form the basal membrane, in addition to producing various growth factors. Thus, being one of the most abundant cells in the stroma, their association with tumor progression has been investigated [41]. It is known that fibroblasts stimulate the progression of malignant epithelial cells, both in vivo and in vitro prostate cancer, based on one of the first studies that identified the relationship [42].

Fibroblasts under normal conditions in the body are quiescent cells that are activated by various stimuli and become vulnerable to epigenetic modifications, which may explain their function as precursors of other cell types [43]. A carcinogenic process in a fibroblast can change its structure and function, promoting a phenotypic characteristic and excessive ECM remodeling [41,44]. Cancer-associated fibroblasts (CAFs) have a different phenotype of normal tissue fibroblasts with increased expression of matrix proteins and abnormal secretion of proteolytic enzymes, which could facilitate the invasive potential of tumor cells [45].

In normal tissue, fibroblasts are responsible for inhibiting the growth of cancer cells, suggesting a role for epithelial growth suppression in a process that requires the direct contact of cancer cells with fibroblasts, which are lost in the conversion to CAFs [46,47]. In tumors, their functions range from stimulating tumor cells to promoting proliferation, migration and invasion, tumor immunosuppression, and secretion of proinflammatory factors. CAFs can produce cytokines and factors that may influence the tumor response, such as the CXCL12 factor, which is closely associated with the increased proliferative capacity of cancer cells [48].

The origin of CAFs may be fibroblasts present in the tissue itself, which have low proliferative activity [49], or through epithelial–mesenchymal transition (EMT), which occurs in processes such as inflammation and cancer. Thus, the epithelial cells themselves may also be precursors of CAFs [50]. This process occurs from the recruitment of epithelial stem cells present in the bone marrow to the tumor microenvironment, which receives signaling cytokines such as transforming growth factor beta (TGFβ), which induces the transformation to CAFs [51,52].

TGFβ is considered a potent inducer of CAF transdifferentiation. These molecules can directly induce the differentiation of these cell types, which induces changes in cytokines, ECM proteins, proteinases, and their inhibitors. Thus, they become responsible for inducing the invasiveness of cancer, but also play a role in how the microenvironment is modulated and influence the process of tumor progression [53].

ECM degradation is also stimulated by CAFs, allowing for tumor cell invasion through the ECM and thereby increasing the metastatic potential of cancer cells. In addition, the increased remodeling in the ECM in cancer is caused by a greater deposition of collagen and fibronectin, a fact supported by CAFs, contributing to tumor invasion with accompanied protease production and release of chemokines, which act as chemoattractants for tumor cells [54].

5. Adipocytes associated with tumors

The influence of adiposity on the increased incidence of cancer has been increasingly discussed and recognized. Obesity not only affects the risk of developing cancer, but also directly influences patient survival [55]. Adipose tissue plays a supportive role by offering thermal insulation and energy storage and is the most abundant tissue in the tumor microenvironment of various types of invasive cancers, potentially participating as a promoter of tumor invasion [56].

Adipocyte functions comprise both physiological and pathological processes, but their role in tumor progression is poorly elucidated. It has been demonstrated that cancer cells in vitro have greater motility and invasiveness in association with adipocytes. Furthermore, in the presence of glucose, these characteristics are more evident due to the increased release of adipocity factors that significantly contribute to tumor progression [57]. Thus, despite the few studies of the role of adipocytes in cancer, it is known that they can stimulate both the growth and survival of cancer cells through metabolic processes. This characteristic is due to the fact that they are recognized as endocrine and inflammatory cells capable of producing hormones, growth factors, and cytokines that act as tumor promoters [58].

Cancer-associated adipocytes (CAAs) can promote the growth and development of tumors secreting anti-inflammatory mediators in an uncontrolled manner and through the release of proinflammatory cytokines, which contribute to tumor maintenance. Although the direct influence of adipocytes in tumor progression is not well known, it is known that the interaction of adipose tissue in the tumor cells leads to poor prognosis, mainly due to their diverse components [59].

Some inflammatory cytokines are produced by CAAs, such as interleukin (IL)-6, tumor necrosis factor (TNF-α), and IL-1β, which facilitate the direct infiltration of inflammatory cells in adipose tissue, leading to chronic inflammation. With this, there is the increased recruitment of macrophages and increased secretion of substances that support cancer progression. Allied with this inflammatory process, there is also the production of reactive oxygen species, which have mitogenic activity and are considered tumor promoters [60]. The inflammatory cytokine IL-6 is produced by a wide variety of cells such as T and B cells, macrophages, fibroblasts, and endothelial cells; in cancer, it is produced by tumor cells and CAAs and is involved in various cellular responses [57].

CAAs can release their entirety by lipolysis in the tumor microenvironment, and these are used by cancer cells for their metabolism, thus promoting tumor growth. An example of such metabolism is the use of fatty acids released by CAAs by tumor cells and the modulation of other cell types such as macrophages and endothelial cells, promoting the formation of a microenvironment conducive to tumor growth [59].

6. T lymphocytes and macrophages associated with defense and tumor progression

Immunity is a complex process that is highly regulated by different cell types and is highly studied and characterized in the tumor context [61]. Immune cell escape is an important characteristic that determines the success of tumor progression. T lymphocytes are one of the most abundant cellular components within tumors, comprising more than 50 % of intratumor cells. Such cells have subpopulations, which impart great heterogeneity, which can directly affect antitumor immunity. In general, T lymphocytes have two major subgroups: cluster of differentiation (CD)4, which are considered helper lymphocytes (T_h), with $CD4^+$ $CD25^+$ $FOXP3^+$ phenotype and $CD8^+$ cells, which directly affect processes such as apoptosis, being considered an antitumor factor and effector [62,63].

T_h cells are divided into T_{h1}, which mainly express the cytokines interferon gamma (IFNγ) and TNF-α, and T_{h2}, which express IL-4, IL-5, and IL-13 [64]. In this context, T-regulatory cells (Tregs) have also been described as a subset of $CD4^+/CD25^+$ cells that act against autoimmune diseases and express the transcription factor Foxp3. Such cells act by suppressing self-reactive T cells; however, they can also be generated by antigenic stimulation, such as infections and cancer [63].

At the tumor site, CD8 T lymphocytes confer cytotoxic effects as CD4 T lymphocytes activate natural killer (NK) cells and antigen-presenting cells. Tumor growth is controlled by CD4 and CD8 T cells [65]. By reducing the expression of major histocompatibility complex surface molecules and human leukocyte antigen in tumor cells, there is minor recognition of these by immune cells, leading to a state of immune escape, characterized by reduced recognition of tumor antigens by cytotoxic T lymphocytes and consequently lower lysis of tumor cells [66]. Immune checkpoints are the main escape mechanism of the immune system, which decrease the cytotoxic activity of CD8 T lymphocytes by the expression of molecules such as programmed death-ligand 1 and cytotoxic T lymphocyte antigen 4 in tumor cells [67].

The presence of Tregs is observed in the suppression of tumor immunity from the recruitment of these cells to the tumor microenvironment by stimuli from facilitative molecules, such as VEGF [29], and also by hypoxia [68,69] and chemokines associated with tumors, such as those in the CCL22/CCL17-CCR4 axis [70,71]. In this environment, specific T cells inhibit tumor antigens, antigen-presenting cells, B cells, and NK cells through the secretion of cytokines such as IL-10 and TGFβ [72]. This allows for the promotion of tumor growth, which poses an important barrier for immunotherapy in cancer [63]. In breast tumors, it has been elucidated that the tumor itself has the ability to recruit Tregs to the microenvironment, guided by the secretion of prostaglandins and signaling TGFβ from cells such as tumor-associated macrophages (TAMs), thereby suppressing local effector cells, which creates an immunosuppressive environment [73].

Macrophages are immune cells responsible for processes related to innate immunity, acting directly in host defense and maintaining tissue homeostasis. These cells are derived from circulating monocytic precursors in target tissues and can polarize in different phenotypes depending on microenvironmental stimuli, such as cytokines, enzymes, and cell surface markers [74]. The major phenotypes of macrophages are activated by the classical (M1) and alternate (M2) pathways. M1 macrophages are involved in antitumor immunity and inflammatory responses characterized by the production of proinflammatory cytokines such as IL-6, IL-12, and TNF-α. In contrast, the M2 phenotype is anti-inflammatory and pro-tumorigenic evidenced by the production of cytokines such as IL-10 and TGFβ, which can be subdivided into subsets M2a, M2b, M2c, and M2d [75].

TAMs and tissue macrophages mobilize for tumors regulated by

different stimuli in the tumor microenvironment. Cytokines, chemokines, and growth factors derived from tumor cells and the stromal microenvironment such as monocyte chemotactic protein-1 (CCL2) are responsible for the recruitment of MACs. Therefore, high expression of TAMs is correlated with CCL2 accumulation in various tumor types [76]. Besides, known macrophage recruitment signals to the tumor site, such as colony-stimulating factor-1 and CCL2, and intrinsic factors of the tumor microenvironment, such as hypoxia and fibrosis, are involved in the macrophage phenotype in cancer progression [77].

It is important to emphasize that TAMs have a modulated phenotype from that during the tumor progression stage, so that it has a phenotype similar to that of M1 macrophages in the initial stages and has characteristics similar to those of M2 macrophages in the advanced stages [78]. Furthermore, TAM infiltration is closely associated with successful tumor progression, since there is no production of substances that facilitate the proliferation of tumor cells, such as MMP-9, which increases the degradation of the ECM and basal membrane by facilitating tumor invasion [79].

TAMs are important in tumor progression, having a function similar to that of M2 macrophages, generating an immunosuppressive microenvironment for the production of cytokines, chemokines, and proteases that facilitate processes such as growth, angiogenesis, and metastasis. This phenotype is characterized by high IL-10 production that favors the induction of genes involved in tumor progression in the cell cycle, apoptosis suppression, and reduction of the cytotoxic microenvironment by reducing the activity of cytotoxic T cells [80–82]. IL-10 is expressed as a TAM and is a major anti-inflammatory and immunosuppressive cytokine present in the tumor microenvironment. In tumor progression, it shows different functions as it prevents the release of other cytokines with antitumor and cytotoxic activity, such as IL-12 and IFNγ, which contributes to immunosuppression [83].

Immunosuppression generated by TAMs is closely associated with the inhibition of cytotoxic T lymphocytes by the production of molecules that act directly by blocking the actions of immune checkpoints and production of inhibitory cytokines, such as IL-10, and by metabolic depletion in the tumor microenvironment. Indirectly, this cell population may also act to prevent the immune function of T cells by recruiting immunosuppressive Tregs or inhibiting the function of dendritic cells, as well as inhibiting the entry of immune cells by regulating ECM factors [77].

7. Therapeutic possibilities for stromal components

The tumor microenvironment is composed of diverse components, and it is essential to understand the interactions between tumor cells and these components, aiming for improved therapies [84]. Thus, the characterization of these stromal components becomes important to allow for the development of new therapeutic strategies that are more targeted and specific [85]. In addition, such information can be used for the development of new pre-clinical experimental models [84].

The evolution of cancer is strongly influenced by the existing association between tumor cells and other components. Thus, the knowledge of the components of the tumor microenvironment has a strong influence on patient prognosis and directly affects the efficacy of anticancer therapies [85]. Stromal cells modify the responses of tumor cells to drugs with profound consequences for therapy, and therefore, it is essential to understand the molecular mechanisms that contribute to these changes because they provide potential targets for improved cancer therapy [86].

The main therapeutic strategies directed against the components of the microenvironment include conventional, combined, and more recently, nanomedicine therapies. In this context, models that are highly similar to the tumor microenvironment, such as tumor explants (chip tumor) or multicellular tumor spheres, have been recently developed [87]. However, it is still essential to conduct new research on the tumor microenvironment aiming at developing new targets against the most

diverse stromal components. Table 1 presents a summary of some of the main strategies used to achieve the tumor microenvironment in cancer therapy.

8. Prospect for stromal identification as a prognosis and predictive factor

Cancer therapy has been developed based on the idea of eliminating cancer cells, either by death or by induction of proliferation standstill. However, we have increasingly discussed the importance of stromal cells and their association with tumor for cell survival [99]. The fact that the tumor microenvironment is composed of various components confers heterogeneity and vast therapeutic possibilities. Characterization of the main members of the stroma allows for the evaluation of potential prognostic markers in cancer and therefore allows a choice for an improved therapeutic approach, which allows for longer survival and improved quality of life for patients with cancer [100].

The importance and influence of stromal components in tumor development and progression is increasingly recognized, and this modulated stroma allows for successful tumor development. Thus, detecting components of the tumor microenvironment is sometimes used to indicate the degree of malignancy and tumor invasiveness, as well as inferences about the prognosis and prediction of disease [101]. In Table 2, some immunohistochemical markers in cancer-potential employees are outlined.

The prognostic significance of microvessel density (MVD) in solid tumors presents results varying between a 75 % and 85 % positive correlation between clinical outcomes in association with different types of cancers. In breast cancer, this indicator is associated with shorter survival and is considered independent, meaningful, and accurate as a prognostic factor, which may reflect the best treatment in these individuals. The prognostic value of MVD in other tumor types is also associated with overall survival [111].

The choice of therapy is also strongly influenced by the tumor microenvironment, since the diversity of stromal components provides a variety of possibilities, which are directed at the control mechanisms that promote tumor progression. Advances in understanding the stromal mechanisms that contribute to tumor progression enable specific therapeutic strategies for this microenvironment. It is important to foster the idea that the interaction between tumor cells and stromal cells in the tumor microenvironment is useful in the identification and screening of potential markers, which may reflect positively in future cancer therapies [112].

9. Conclusions and future perspectives

The high incidence of cancer in the human population indicates that their study is relevant to identify possible new therapeutic and diagnostic forms and understand that cancer is not caused by a single event; rather, cancer arises from an accumulation of mutations and epigenetic and environmental factors associated with cells in the environment in which the tumor plays an important role.

The tumor stroma facilitates the invasion of cancer cells and their survival in the environment and causes the body's cells to change their functions to respond to the new body being created. Fibroblasts, adipocytes, macrophages, immune cells, endothelial cells, and the ECM are the main components of the stroma, which have altered functions to allow for tumors to invade tissue and progress.

New forms of therapy and diagnosis are being established based on studies of the tumor stroma and their components, considering new targets in the fight against cancer. The use of new information about the behavior and interactions between tumor cells and the stroma allow for new approaches, taking into consideration the relationship of these components with invasion and tumor progression. Faced with this situation, it is important that additional research in this area is carried out, thus enabling the identification of new stromal components by

immunohistochemistry because of the ease of insertion in clinical practice, when compared to other diagnostic techniques. These forms, with less aggressiveness in cancer treatment, could enable a better quality of life and increase survival in patients.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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