Chapter 2
Immune Response and Tumor Microenvironment

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ABSTRACT

Tumor formation and progression are caused by neoplastic cells, which take advantage of interfere with cellular processes that control growth, survival, and division. New research emphasizes the critical role of the tumor microenvironment (TME) in cancer initiation and metastasis, even though genetic and epigenetic changes are well-known malignant transformation. The tumor microenvironment (TME) influences tumor metagenesis, angiogenesis, and immune tolerance, which helps cancer cells proliferate rapidly. It also plays a critical role in the origin, progression, and invasion of cancer. With a variety of roles, including matrix deposition and remodeling, extensive reciprocal signaling connections with cancer cells, and crosstalk with invading leukocytes, cancer-associated fibroblasts (CAFs) are an essential part of the tumor microenvironment. This chapter reveals the origins of CAFs and the heterogeneity of CAF function, wherein it is preferable to preserve some antitumorigenic properties.

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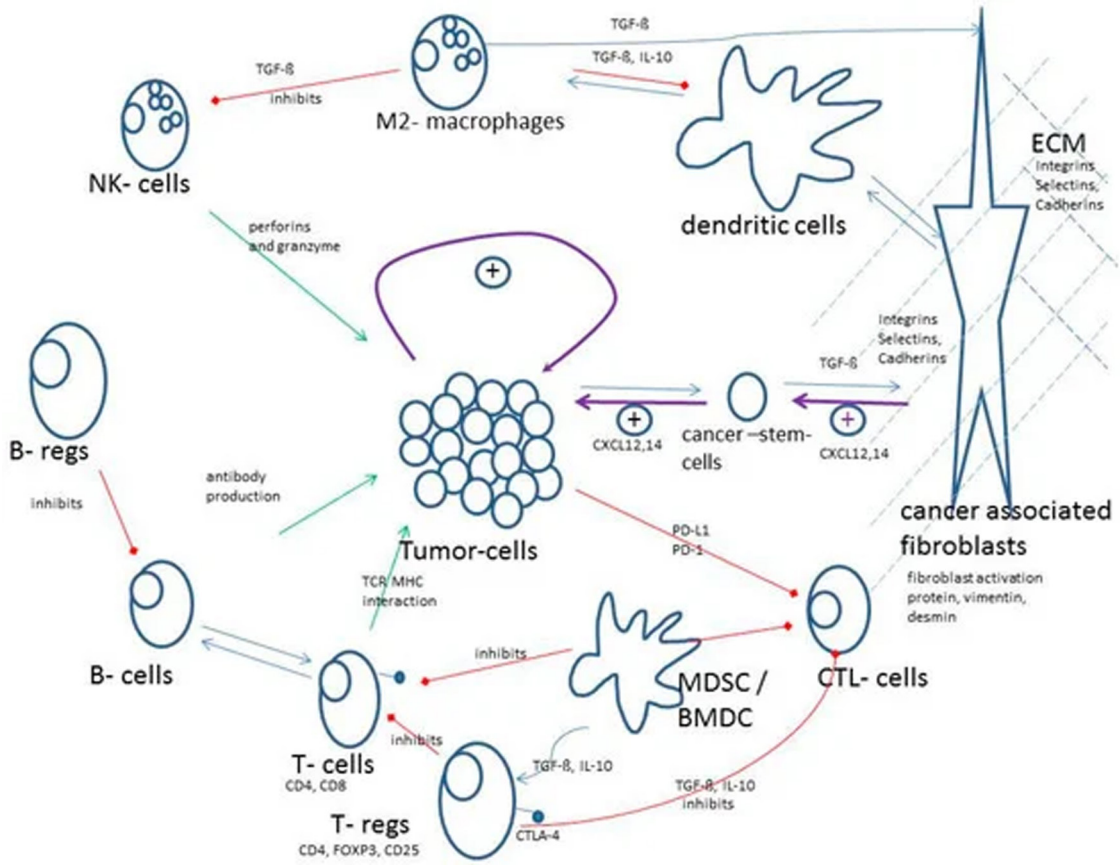
INTRODUCTION:

Cancers develop through a variety of genetic and epigenetic mechanisms, including clonal selection and expansion inside the tissue ecosystem's adaptive landscapes. Neoplastic cells have demonstrated for several decades their ability to take advantage of, subvert, and interfere with cellular processes that control cell growth, survival, and division, which results in the development and spread of tumors. The most well-known origins of malignant transformation are genetic and epigenetic changes that result in stem-cell-like characteristics, like unrestricted cell division and inhibited differentiation, (Cassim & Pouyssegur, 2019). More and more research are pointing to the interaction between tumor cells and their surrounding microenvironment as a critical factor in the initiation and spread of cancer. The stroma, nerves, blood and lymphatic vessels, and immune system cells- which may be resident in the affected tissue or drawn from its periphery make up the tumors's microenvironment, (Hendry *et al.,* 2016). Teaching the immune system to identify and eliminate cancerous cells is known as cancer immunotherapy. This tactic can potentially destroy tumor cells selectively and systematically and create memory responses that can be used to prevent recurrent illness. Paul Ehrlich developed his "immune surveillance hypothesis" at the start of the 20th century, which gave rise to the idea that the immune system is capable of identifying and eliminating specific foreign invaders, (Van der Jeught *et al*., 2015). Immune populations other than T cells are being studied to mediate the efficacy of immunological treatments. Additionally, B cells are more prevalent in PCa tissues than in benign prostatic tissues, and an increase in the number of B cells within the prostate tumor microenvironment (TME) has been associated with a more aggressive course of the disease. B cells can produce lymphotoxin after being recruited, which triggers IKKA-STAT3 and /or BGI 1 signalling in cancer clones that remain after surgery, speeding up the development of castration resistance for PCa, (Kwon, Bryant, & Parkes, 2021). Endothelial and Fibroblast cells, as well as a variety of immune cells, make up the tumor cell's microenvironment, with which they interact continuously. Immune checkpoint blockade (ICB) response has been demonstrated to be influenced by the makeup of the tumor microenvironment (TME), (Petitprez *et al*., 2020). TME composition is dynamic and changes as a result of ICB treatments. The TME has evolved differentially in responders and non-responders, according to several studies. In long-term studies involving ICB-treated melanoma patients. T cells which are classified as adaptive immune cells are the cells that are most frequently seen in human tumor tissues. T cells can influence the growth of cancers by directly interacting with tumors or by stimulating other cells in the tumor microenvironment notably this trait has been applied to therapeutic contexts to increase the anti-tumor efficaciousness of treatments such as ex vivo modified T cells transduced with the chimeric antigen receptor car or T-cell-inhibitory PD -1 receptor inhibition for example tumor acidity was thought to serve as a sort of protection armor enabling cancer cells to simultaneously thwart the actions of all immune effectors that are agents that combat tumors and convert tumor-supporting regulative immune cells another significant example is the hypoxic tumor microenvironment which inhibits and neutralizes T cell responses and functions, (Cassim & Pouyssegur, 2019). Immunotherapy works by using particular checkpoint medications to stop the proficiency of a neoplasm and suppressive interactions between the patient's immune system. prostate cancer outcomes are still quite bad despite immunotherapy showing increased results in many cancer types. prostate cancer results in a deficiency of t-cell defense mechanisms by the immune system against malignant cells still a very tiny percentage of individuals do benefit from checkpoint inhibitors when it comes to immunotherapy reactions there have been more positive results from studies on the tumor microenvironment of prostate cancer especially for CRPC. in the clinical trials of PD 1 and CTLA 4 inhibitors the therapy of mCRPC has shown modest

potency when combined with enzalutamide an anti-androgen permitted for use in mCRPC when taken in people with CDK12 mutations these inhibitors do. However, also demonstrates favourable outcomes as new immune biomarker assays for prostate cancer are used future years should show continued improvements in the effectiveness of immunotherapy, (Melo *et al.,* 2021). Mechanism and Interaction of Tumor Microenvironment was shown in Figure 1. The tumor microenvironment states the initiation of the cancer cells, development, progression, and termination, (Arneth, 2019).

Figure 1. Mechanism and interaction of Tumor Microenvironment (TME) (Arneth, 2019)



The tumor microenvironment is an extracellular environment in which the tumor cells are identified where the stem cells in a tumor would outgrow and develop tumor angiogenesis. The TME is surrounded by the cellular components including the immune cells, blood vessels, fibroblasts, and inflammatory cells (Spill *et al.,* 2016), along with the malignant and non-malignant interactions that determine the cancer initiation, development, and progression, (Balkwill, Capasso, & Hagemann, 2012) (Hanahan & Coussens, 2012). The invasion of healthy tissues occurs through the circulatory and the lymphatic system in terms of the malignant cells. The tumor usually communicates signals from the microenvironment closely related to the organs by the lymphatic or circulatory system, (Arneth, 2019) The tumor cells will be influenced by the signals that induce the immune response tolerance and the faster outgrowth of the

tumor angiogenesis, (Korneev *et al.,* 2017). The TME is the most complex, and the dominant complex of a tumor therefore understanding the pathway, processes, and their interaction surrounding the micro-environment is critical in the progression of heterogeneous complex components in the development of various cancers, (Arneth, 2019). The progenitor parenchymal cells act as the tumor-initiating complex cellular signalling environment that supports widely to spread of the tumor cells and various other mechanisms that are implicated by the tumor-mediated signalling and also the modulator inflammatory responses. A research study shows that TME influences tumor mutagenesis and tumor cell development, and their invasion affects the physiological condition of homeostasis in the normal tissues, (Korneev *et al.,* 2017) (Walker, Mojares, & del Río Hernández, 2018), that shows the components of the immune cells as complex components of the TME which leads to the development and faster outgrowth of the cancer cells. Furthermore, researchers also found that TME is also used to protect cancer stem cells, (Mills, Lenz, & Harris, 2016).

The tumor microenvironment has the immune checkpoint blockade which can suppress the antitumor T-cell activity by the various inhibitory receptors and the ligands that are expressed by the tumor cells for the proliferative cancer cell activity, (Van der Jeught *et al*., 2015). In recent studies, a specific type of immunotherapy has been developed that targets the immune checkpoint molecules using a specific monoclonal antibody that targets molecules such as the cytotoxic T lymphocytes and the programmed cell death associated proteins to advance the disease stage in the metastasis cancer cells the tumor-infiltrating lymphocyte and the CD8+ T cells serves the important relevant factor in response to the tumor microenvironment for the prognosis of treating various cancer treatments. The pathways associated with the TME immune cells, and their signalling pathways are being profiled for the immune and signalling pathways using the immune response associated and the driver gene expression pattern data with the genetic mutations such as the TP53, EGFR, and BRAF, (Kondou *et al.,* 2019). The tumor cells determine the composition through the release of the growth-stimulating factors along with the release of cytokines and chemokines that manipulate the TME cell functions and their interactions with their surroundings. The immunosuppressive tumor environment works with the help of stromal cells which includes diversified cell components such as the Mesenchymal stem cells (MSC), the cancer-associated fibroblasts (CAFs), and the cancer-associated endothelial cells (CAECs). They promote immune suppressive cell development, proliferation, and differentiation with the release of cytokines and chemokines along with the other metabolites. The tumorigenesis and the progression of tumors by the specific macrophages are solely responsible for the maintenance of the homeostasis of tissues. The regulatory B cells which arise from the B cells upon a certain type of differentiation attract the tumors to release the chemoattracts and to suppress the immune-inflammatory responses by secreting some of the immunomodulatory cytokines and interactions with the cell surroundings, (Cortellino & Longo, 2023). The imbalance of Th1 and Th2 results in the cancer development and progression due to the escape mechanism from the immune system by the tumors, (Shang *et al*., 2024). The Th2 cells contribute to the fibrosarcomas in the tumor progression by the secretion of IL 4, and IL5 and promoting the tumor cell migration, (Kuwabara *et al*., 1995) (Li *et al.,* 2008). The immunosuppressive regulatory T cells (Tregs) are recruited to the tumor region as the tumor cells would select and recruit the tumor microenvironment cells by the release of certain specified hormones to modulate their immunosuppressive activity through surface receptors and the interactions of hormones and the metabolites. Also, the cancer cells would decide the suitable tumor microenvironment through the selection of some of the soluble factors and the recruitment of the immunosuppressive cells like the monocytes that migrate to the tumor microenvironment and are attracted to the chemokines such as the CXCL 12, and CXCL1 that are released by the cancer cells, (Cortellino &

Longo, 2023). The cancer cells accumulate various mutations in the tumor suppressor genes that lead to increased signalling pathway activation, which tends to cause the tumor cells to remain partially independent of growth factors. The spatial pattern of the immune cells concerning tumor cells will have the highest impact on the Tumor Immune MicroEnvironment (TIME) which is complex and inhibits the pro-tumor and anti-tumor effects, (Shang *et al.,* 2024). The Tumor Immune MicroEnvironment (TIME) is influenced by the behavioral factors of tumor cells such as proliferation, invasion, and angiogenesis, and their resistance to the drug is mediated by the interaction between the immune system and the cells in the microenvironment, (van der Jeught *et al.,* 2015).

The anticancer therapy focusing on the target metabolic reprogramming of the tumor cells can have a higher ability to survive and induce the role of signalling pathways in driving the responses of immune cell-derived factors in the tumor microenvironment along with performing the therapeutic strategies on targeting the major pathways in tumor cells might help for responses on anti-tumor immune responses, (Wegiel *et al.,* 2018). And providing a comprehensive study on how TME-based markers can respond to specific immune responses. In addition, the immune checkpoint blockade has now emerged providing a response and resistance to emerging treatments. By focusing on the tumor cells one can able to manipulate the tumor environment and assist therapy-related systemic responses. The evolution of research in cancer can depict the development of strong memory responses by blockade of immune checkpoints and neutralizing the immune modulatory cytokines in cancer treatment can bring a clear benefit for cancer patients in the upcoming years, (van der Jeught *et al.,* 2015).

1. TUMOR IMMUNE MICROENVIRONMENT:

Tumor cells, immune cells, and cytokines make up the tumor immune microenvironment. Anti-tumor and pro-tumor interactions among these elements determine anti-tumor immunity cells, (Locy *et al.,* 2018) (Lv *et al.,* 2022). Effector T-cells, such as cytotoxic CD8+ and CD4+ T cells, natural killer cells (NK), dendritic cells (DC), and M1 polarized macrophages are among the immune cells linked to tumors. The natural killer T Type 2 cells are the tumor-derived N2-polarized neutrophils.

1.1 Anti-Tumor Immune Cells:

T-cells are mainly responsible for the anti-tumor immune response, including cytotoxic T lymphocytes (CTL) and T helper cells. The cytotoxic T lymphocytes usually recognize the MHC-I molecules expressed by the tumor cells which induce apoptosis by chemokines. The CD4+ T cells can promote the activity of cytotoxic T lymphocyte proliferation activity, increase the dendritic cells' antigen presentation, promote CTL activation, and increase CTL memory conformation.

The most specialized antigen-presenting cells (APC) are the dendritic cells, which stimulate naïve T cells to start adaptive immunological responses. The Dendritic Cells produce CD80 or CD86, which increase the T cell activation by interacting with CD28 to generate the costimulatory signals and to produce TNF-α, IL-6, and IL-12, (Böttcher & Sousa 2018). to participate in anti-tumor immunity actively. The tumor cells tend to lose the MHC-I molecule-dependent antigen presenter, which is required to activate CD8+ T cells. By binding to MHC-I, inhibitory receptors prevent natural killer cells from activating, allowing them to use the "missing self" strategy to exclude targets that express MHC-I molecules, (Myers

& Miller, 2021) (Cózar *et al*., 2021). The M1 macrophage releases are directly intermediated through cytotoxicity by removing the antitumor effects.

1.2 Tumor-Promoting Immune Cells:

Peripheral tolerance and immunological homeostasis are crucially dependent on tregs. By producing immunosuppressive cytokines including IL-10 and TGF-BETA, the Tregs work to reduce the anti-tumor immune response in the TIME. Tregs can also induce NK cells and cause cell death CD8+T. M2 macrophages secrete different immunosuppressive cytokines such as the TGF-BETA, IL-4, and IL-13. The Th2 immune response is activated when M2 macrophages are involved. TGF-beta suppresses the CD8+T cell-mediated anti-tumor immune response, while Tregs block the tumor-mediated cytotoxic T lymphocyte response by severing the TGF-beta-dependent cell contact. Additionally, it suppresses CD8+T cell memory formation via CTLA-4. Major MHC class II ligands are present in LAG-3. These Tregs support enhancing the function of myeloid-derived suppressor cells that are identified as the monocytic and polymorphonuclear subsets so that they contribute to establishing an immunosuppressive tumor environment.

2. TUMOR CELLS AND THEIR FUNCTION

Tumor cells play an important role in the Tumor Immune Microenvironment they can directly inhibit the functions of the immune cells by creating a microenvironment and secreting tumor antigens and chemokines for capturing inhibitory cytokines, and secretion of the VEGF, which can suppress the dendritic cells from maturation and help in the activation of the regulatory T cells and enhances the activation of immune checkpoints. TIME is broadly populated with voids of the cytotoxic T lymphocytes, termed the Infiltrated-Excluded Tumor Immune Microenvironment, as they are present in the outer of the tumor mass in the fibrotic cells. They are mostly associated with various diagnoses of cancers such as colorectal carcinoma, melanoma, and tumor-associated macrophages (TAM) to prevent Cytotoxic T lymphocyte infiltration into the core of the tumor cells. There are three classes of the TIME: Infiltrated excluded, Infiltrated-inflamed, and Infiltrated-TLS. The I-E TIMEs can be characterized by the elimination of CTLs from the tumor core. The CTLs are present in the periphery of the tumor where it comes in contact with the tumor-associated macrophages. The I-I TIMEs have an abundance of expression of the PD-L1 on tumor and myeloid cells, (Binnewies *et al.,* 2018). Tumor stoma (TS), where more stromal components are located in the tumor core, and tumor core (TC), which houses the majority of the tumor cells in the tumor border, make up the three main sections of the tumor tissue compartments. A zone that forms between the tumor core and the tumor stoma is known as the invasive margin, (Fu *et al.,* 2021).

The tumors are well established in the pro-tumor and immunosuppressive environment to support the growth and their immune evasion. They aim to build an immunosuppressive TIME that produces signalling pathways that lead to the production of cytokines and chemokines with significant effects. It has been shown that the BRAF has shown expression of factors IL-10 which induces the cancer-associated fibroblasts (CAF). Because of their ability to prevent tumor growth in a variety of epigenetic malignancies, macrophages are important players in the TIME around blood arteries. Chemokines and cytokines in the tumor microenvironment will draw blood from the immune cells circulating throughout the tumor cells' growth.)

The immune cell distribution within tumors is made up of some well-organized immune cell structures, such as Tertiary lymphoid structures (TLS), which are hyperplasia lymphoid tissues that are found outside immune organs and may be present in particular cell fractions. They are made up of mature dendritic cells from the rich T cell zone, high follicular dendritic cell density in B-cells, and antibodies. Within the tumor, the spatial blood flow, or heterogeneous blood flow, would create more niches, each involving a unique biological activity that would give growth factors, nutrients, and oxygen, (Fu *et al.,* 2021).

3. CONSTRUCTION OF THE TIME:

3.1 Tumor Initiation:

The spatial distribution of immune components in precancerous normal tissues has been explored in various research, and it has been found that during tumor start, normal cells can accrue a sequence of mutations,. (Li *et al.,* 2020) (Yoshida *et al.,* 2020). The cell mutations will demonstrate immune surveillance and trigger the immune response, thereby excluding the nonself cells found in the specific areas where this precancerous transformation takes place. The immunosuppressive microenvironment, where immune cell heterogeneity affects tumor-infiltrating immune cells, is primarily responsible for the activation of the STAT-3 signalling pathway by decreasing immune cell infiltration and the cytokine interleukin-6, (Smola, 2019). This has to do with how normal cells change into tumor cells and CTS.

3.2 Establishment of Primary Tumors:

The character of the T cells is the major factor that determines the tumor progression within the TIME. The T cell dysfunction will lead to T cell exhaustion. As the anti-tumor T cells cannot control tumor growth they opt for the tumor-induced tolerance mechanism. This T-cell exhaustion can be observed in chronic viral infections and multiple types of cancers. They are characterized by the expression of high surface inhibitory receptors like the CTLA-4, PD-1, and TIM-3 on the T cells. The prevention of t-cell exhaustion can be a long-term tumor-controlling process to target the pathways such as the immunosuppressive TIME to obtain the anti-tumor t-cell responses, (Binnewies *et al.,* 2018).

3.3 Time During the Progressive Tumor Development:

Due to the chronic antigen exposure on the T cell exhaustion occurs rapidly after the initiation of the oncogenes. As the T cell transition occurs from the effector T cells to exhausted T cells where there will be an increased expression of the molecules associated with the exhaustion such as the LAG3, TIM3 and due to some of the downregulation of the effector cytokines. During the tumor development, increasing changes in the quality of TIME would occur that usually coincide and influence responses. As the tumor progresses the Monocyte-derived counterparts (TAMs) of both the effector T cells become exhausted T cells and the dendritic cells become more marginal. The neutrophils have been linked with both the

metastatic stages of success and failure where the macrophages serve as the pro-metastatic function in the tumor cell because they lead to metastatic failure.

Tumor-tumor interactions, which are facilitated by growth factors and cytokine secretion to create a new tumor microenvironment, have been shown to support invasion, metastasis, and inflammation as well as the infiltration of tumor tissues by TAMs and myeloid-derived suppressor cells. A tight relationship with the bone marrow-derived cells and the cancer-associated fibroblasts would be necessary at every step of the metastasis. The primary agents that contribute to immunosuppression and immune-mediated tumor progression include cytokines, chemokines, and growth factors. These released substances attract a large number of cancerous cells that proliferate and send out signals to live, supporting the milieu that allows tumor spread, (Binnewies *et al.,* 2018).

Inflammation and immune suppression:

(The inflammation is induced by the oncogenic stress produced in the tumor microenvironment or by some tissue damage that can contribute to the initiation, and progression of the epigenetic disease), (Binnewies *et al.,* 2018). (The inflammation is acute, and the chronic effect is produced on healing and tissue health. It is the line of defense that is characterized by the influx of plasma and cytokine-secreting immune cells that are hired at the time of the tissue injury to heal the damaged tissue.) and by the pro-inflammatory action, it is terminated through the regeneration of the cell proliferation and new tissue, (Smith & Kang, 2013) (Lowe & Storkus, 2011).

(As in the case of solid malignancy chronic inflammation does not initiate the growth of the tumor but fosters the tumor progression and metastasis by providing a suitable environment for the invasion to take place. Due to the release of the pro-inflammatory molecules such as the IL-1 promoted by the primary tumor, it certainly undergoes necrosis to promote angiogenesis and release growth factors.)

The IL-10 secreted by the tumor tissue has been shown to inhibit the activation of dendritic

Cells. Then Tregs are considered potent suppressors similar to the regulatory B which plays an important role in tumor progression in metastasis. The IL-10 suppresses the anti-tumor immune response to promote the function of Tregs and the mechanism to inhibit the responses of effector T and NK cells. The tumor microenvironment can alter the function of B cells and Dendritic cells to promote tumor progression. Chronic inflammation alters the environment of the tissue affected by abundant growth factors, cytokines, and chemokines to promote metastasis including the mast cells, tumor-associated macrophages, and dendritic cells that have tumor-promoting properties during each stage of the metastasis progression, (Binnewies *et al.,* 2018).

3.4 Immune Environment in The Metastasis:

Based on the epithelial-to-mesenchymal transition: The tumor-promoting immune cells that are recruited that contribute to each stage of the tumor progression and metastasis. The EMT cells are cells characterized by cell-to-cell adhesions. Tumor-promoting cytokine production, immune cell recruitment, and the chronic cycle have all been linked to malignant EMT. In the inflammatory tumor microenvironment, which provides the immune cells that promote tumor growth, the tumor cells release chemokines and immune cells. Following invasion, the cytokines generated help to trigger the extracellular matrix (EMT) state, in which immune cells are drawn to the tumor tissue and secrete proteases. Additionally, they regulate tumor-intrinsic factors that encourage vascular permeability and intravasation, where

immune cells mediate the migration of platelets, lymphocytes, and inflammatory chemokines into the circulation, protecting the tumor cells from immune-mediated cell recognition and stress. By coming into direct contact with neutrophils, cytokines are able to extravasate and stimulate the expression of sticking proteins such ICAM-1, which helps to facilitate extravasation at the metastatic location, (Binnewies *et al.,* 2018).

Tumor-infiltrating immune cells secrete cytokines and chemokines that facilitate epithelial-mesenchymal transition (EMT). These cells include macrophages and lymphocytes, which can trigger the EMT by triggering signalling pathways involving TGF-beta, TGF-alpha, and other stroma components that are able to regulate in the environment of a chronically inflamed tumor, (Binnewies *et al.,* 2018).

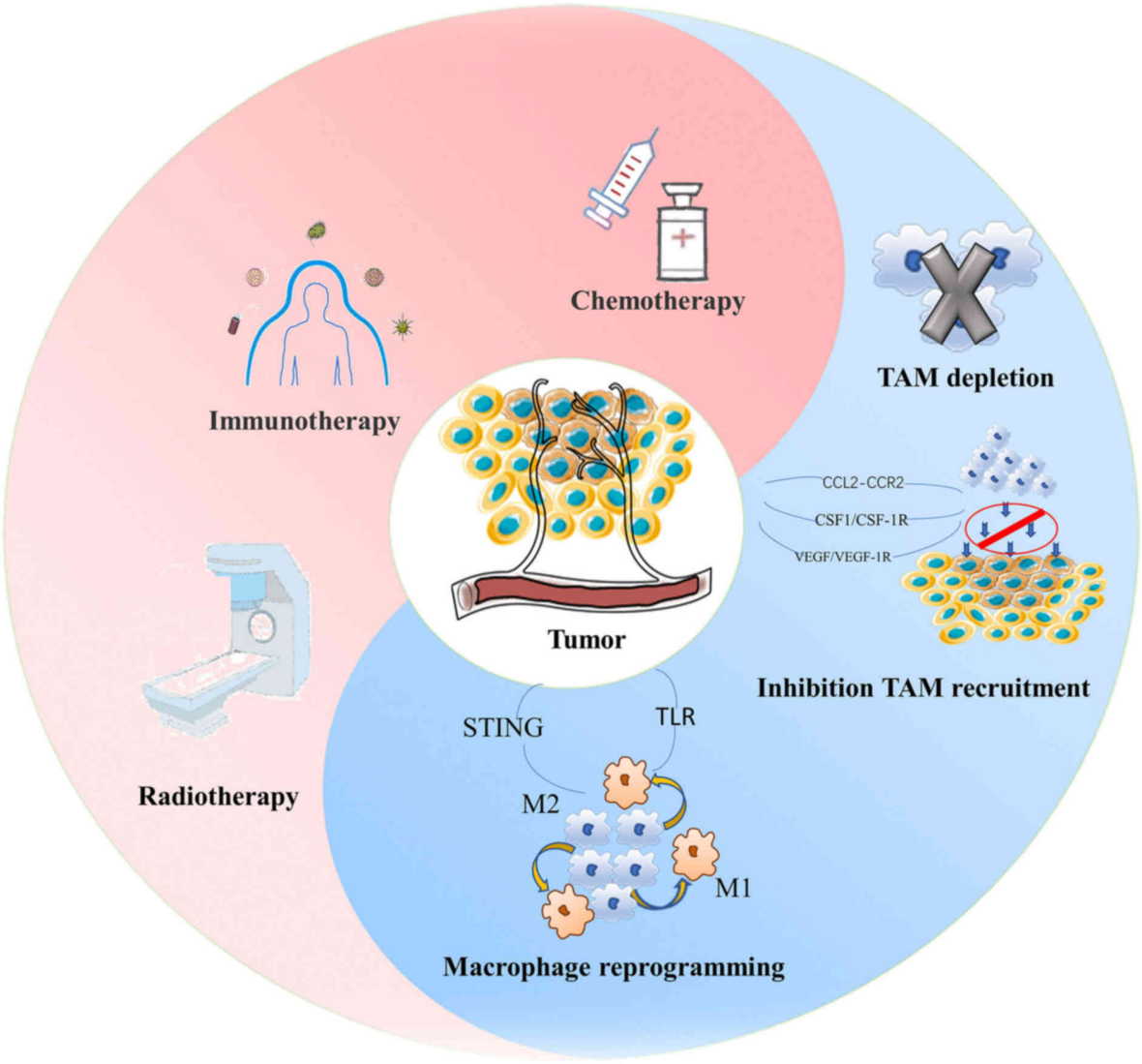
Cancer-associated fibroblasts are not immune cells because they are stromal cells that infiltrate tumors. By secreting pro-inflammatory cytokines, they aid in the EMT and the advancement of cancer. By forming relationships with malignant epithelial cells, which display epithelial cells from activated fibroblasts, MSCs or fibroblasts learn to promote tumors, (Binnewies *et al.,* 2018).

4. CHARACTERISTICS OF TUMOR MICROENVIRONMENT

The Tumor microenvironment consists of multiple constituents, such as tumor parenchyma cells, fibroblasts, mesenchymal cells, blood, and lymph vessels, in addition to immune cells, chemokines, and cytokines that infiltrate the tumor. These many and diverse components meet the criteria for a complex system, as defined by the multilevel, multiscale, and nonlinear dynamics of interactions between the constituents. Every single one of these elements has the potential to significantly impact the growth and development of tumors. These elements can all play significant roles in the initiation and spread of tumors. Tumor associated fibroblasts are one of these non-immune constituents that are in charge of creating and modifying the extracellular matrix. As a tumor grows larger, it is essential for the tumor to continue growing new blood vessels, and existing blood and lymphatic vessels can serve as pathways for both local invasion and distant metastasis. Numerous investigations have demonstrated that poor patient survival is predicted by high blood vessel density and the production of factors that promote blood vessel formation, such as matrix metalloproteinase (MMPs), platelet-derived growth factor (PDGF), and vascular endothelial factor (VEGF), (Chew, Toh, & Abastado, 2012). Alterations in homeostasis and an aberrant immune response control the development of tumors. Interactions between cancer cells and immune cells in the TME influence cancer growth and metastasis. The TME controls fundamental tumor cell survival and enhances tumor cell function. TME cellular and structural constituents interact to promote the aggressive and metastatic spread of cancer cells to remote locations. A growing body of research suggests that the presence of innate immune cells in the tumor microenvironment (TME), such as macrophages, neutrophils, DCs, innate lymphocytes, myeloid inhibitory cells, and adaptive immune cells, such as T cells and B cells, can accelerate the growth of tumors, (Wang *et al.,* 2023). Tumor growth is influenced in both directions by the complex and unique environment known as the tumor microenvironment (TME), which is made up of interconnected elements. The TME primarily consists of immune cells. Macrophages are a significant subset of immune cells that can undergo phenotypic and status changes as a tumor progresses. Tumor growth is impacted by these modifications in two ways. Thus, it makes sense to target macrophages as a component of an antitumor strategy. Macrophages exhibit significant heterogeneity and plasticity. M1 macrophages are thought to have an antitumor role in the early stages of tumor progression and to eventually change into M2 macrophages, which promote tumor

growth. TAMs are typically M2 macrophages, (Xu *et al*., 2022). Figure 2 illustrates the techniques for focusing on macrophages in conjunction with traditional cancer treatment. TAM depletion, inhibition of macrophage recruitment, and macrophage reprogramming are the three basic tactics used to target macrophages. It is anticipated that combining these tactics with immunotherapy, chemotherapy, and radiation therapy will enhance the therapeutic outcome for cancer: tumor-associated macrophage, or TAM, (Xu *et al.,* 2022).

Figure 2. Techniques for focusing on macrophages in conjunction with traditional cancer treatment



According to Dvorak (1986), tumors are frequently referred to as “wounds that never heal” because of the many similarities between their stroma, including fibroblast activation, increased intensive remodeling procedures and the synthesis of extracellular matrix (ECM) proteins. Molecularly, biochemi-

cally, and pathologically, the activated stroma differs from the normal stroma, (Liu *et al.,* 2019). Tumor microenvironment (TME) plays a pivotal role in immune evasion, tumor differentiation, epigenetics, and dissemination. The TME is actually a very diverse environment made up of various cell types and a large number of abundant molecules that are produced and released by immune, stromal, and tumor cells, (Labani-Motlagh, Ashja-Mahdavi, & Loskog, 2020). The TME contains immune cell populations, extracellular matrix (ECM), mesenchymal stroma/stem-like cells (MSCs), cancer-associated fibroblasts (CAFs), cancer-associated adipocytes (CAAs), and cancer-associated endothelial cells (CAECs). These cells enhance the growth, survival, and dissemination of tumor cells by secreting signalling chemicals and extracellular matrix components, which also have immunosuppressive properties. The TME contains immune cell populations, extracellular matrix (ECM), mesenchymal stroma/stem-like cells (MSCs), cancer-associated fibroblasts (CAFs), cancer-associated adipocytes (CAAs), and cancer-associated endothelial cells (CAECs). These cells enhance the growth, survival, and dissemination of tumor cells by secreting signalling chemicals and ECM components, which also have immunosuppressive properties, (Cortellino & Longo, 2023). There is a chance that the balance of immunosuppressive and immunosupportive factors within the tumors can be influenced by the cytokine content in the microenvironment. Studies have shown that targeting cytokines to tumors can alter the microenvironment and improve the efficiency of other immunotherapeutic treatments, (Luo *et al.*, 2021). The tumor -immune cells, endothelial cells, fibroblasts, and metabolites. This might be primary or metastatic. The TME plays a crucial role in ovary cancer by facilitating peritoneal metastasis through the co-evolution of cancer and stromal cells. This includes neutrophil influx into the omentum and the extrusion of neutrophil extracellular traps (NETs), making the premetastatic omental niche suitable for implantation. This is a necessary step for peritoneal metastasis in orthotopic models of ovarian cancer, (Luo *et al*., 2021). TME cell populations can impede immune response, making them potential targets for therapy in hematological and solid cancers, including carcinomas, (Bejerano, Jordão, & Joyce, 2021). Tumor cells cause considerable changes in the surrounding environment, including molecular, cellular, and physical changes. This means that the cellular makeup of the tumor microenvironment (TME) is constantly changing and can become more complex as tumors grow. Furthermore, the cellular makeup of the TME of different tumor types varies; yet, immune cells, stromal cells, blood vessels, and an extracellular matrix are a continuous feature of the TME of cancer. During early tumor growth, cancer cells and the TME have a dynamic and reciprocal connection. These interactions have an impact on cancer-specific immune responses, local invasion, and metastatic dissemination. Tumors are invaded with a variety of adaptive and innate immune cells that can conduct both pro- and anti-tumorigenic roles. Furthermore, their activities play an important role in modulating or inhibiting host antitumor immune responses in the TME, (Melo *et al.,* 2021). But in the last few years, the TME's immense complexity has become apparent, and these early perspectives might now be viewed as overly optimistic. Depending on the organ in which the tumor originated and the stage of cancer growth, the TME's cells may be tumor-suppressive or tumor-supporting. The type of malignancy, TME cell ontogeny, and the cells' "education" inside the tumor mass and/or throughout the body all have an impact on these competing roles, (Bejerano, Jordão, & Joyce, 2021). Comprising tumor cells and stroma, TME is often marked by elevated interstitial fluid pressure, glutamine addiction, hypoxia, accelerated aerobic glycolysis (Warburg effect), low extracellular pH (pHe), and abnormalities in vascular function. Recent evidence suggests that metabolic reprogramming occurs during tumor development and progression, potentially enhancing the ability of stronger malignant cells and malignancies to readily adapt their metabolism to the most advantageous pathways—beyond the Warburg effect—to ensure their growth and survival in response to varying environmental stimuli, like hypoxia or limited

nutrient supply. Changes in the metabolic composition of tumors may affect the level of cellular differentiation and cell signalling, (Ramamonjisoa & Ackerstaff, 2017).

5. CONSTITUENTS OF TUMOR MICROENVIRONMENT:

The ability of the tumor microenvironment to maintain proliferative signals, avoid growth suppressors, initiate invasive metastases, permit replicative immortality, initiate angiogenesis, and withstand cell death are its defining characteristics, (Hanahan & Weinberg, 2011). Drug targets and its mode of action was listed in Table 1.

Table 1. Therapeutic targets for cancer

DRUG TARGETS	MODE OF ACTION
Cyclin-dependent kinase inhibitors	Evading growth suppressors
Immune activating anti-CTLA4 mAb	Avoiding immune destruction
Telomerase inhibitors	Enabling replicative immortality
Selective anti-inflammatory drugs	Tumor promoting inflammation
Inhibitors of HGF/c-Met	Activating invasion and metastasis
Inhibitors of VEGF signalling	Inducing angiogenesis
PARP inhibitors	Genome instability and mutation
Proapoptotic BH3 mimetics	Resisting cell death
Aerobic glycolysis inhibitors	Deregulating cellular energetics
EGFR inhibitors	Sustaining proliferative signalling

(Hanahan & Weinberg, 2011).

Tissues which are deregulated by tumor microenvironment are subjected to high chronic inflammation and mostly exhibits high cancer in a respective study when liver cirrhosis patients die hepatocellular carcinoma is the primary cause of mortality important modulators of carcinogenesis are tumor-associated macrophages (TAMs) and they are derived from bonemarroe and spleen. Macrophages help in immunity defense with the help of tumor-associated macrophages tumor progression occurs. TAMs' effects in the hypoxic region of growing tumors lead to angiogenesis and the emergence of an invasive phenotype, while macrophage chemoattractants such as VEGF and endothelin-2 drive their overexpression, (Quail & Joyce, 2013).

Studies have shown that both human and murine tumors contain natural killer (NK) cells, macrophages, mast cells, infiltrating lymphocytes, dendritic cells, eosinophils, and immature myeloid cells, also known as myeloid-derived suppressor cells (MSDC). These immune cells are located in secondary lymphoid organs and function as a cellular component of tumors. The ability of immature myeloid cells to differentiate into macrophages, DCs, and endothelial cells is a result of their reaction to potent pro-angiogenic stimuli provided by tumor cells. The U.S. Food and Drug Administration (FDA) approved ipilimumab, a monoclonal antibody that targets CTLA-4, to treat patients with metastatic melanoma. It also exhibits the similar outcomes as the target PD-1, (Kerkar & Restifo, 2012).

The primary constituents of the tumor microenvironment are extracellular matrix, vasculature, immune cells, and tissue-associated endothelial cells. When the vasculature of tumors and normal blood cells is compared, it can be shown that the tumor has altered both structurally and functionally, decreasing the amount of nutrients accessible and influencing the hypoxic area. A tumor's cells are more likely to survive and grow resistant to apoptosis when there is hypoxia present. The stromal cells known as cancer associated fibroblasts (CAFs) comprise a substantial amount of the tumor microenvironment. They send out signals that encourage the growth of tumors and allow small groups of cancer cells to evade treatment. The activated CAFs are derived from resident fibroblasts, and they help in the synthesis and secretion of extra cellular matrix and the release of proteolytic enzymes. Immune cells are of two types of two types innate and adaptive these cells interact with the tumor cells through direct contact or by chemokine and cytokine signalling which effects the shape and behaviour of the tumor cells and the therapy response. Tumor-associated endothelial cells (TECs) differ from normal endothelial cells in many aspects such as proliferation, migration, and response to growth factors and chemotherapeutic drugs. The extracellular matrix of the tumor stroma is altered when compared with normal tissue that is produced by all the cells of TME, which results in a closed fiber network it effects the ability of tumor cells to invade and metastasize and affects the sensitivity to drug treatment, (Wu & Dai, 2017). The major building block of adipose tissue is the adipocyte, which serves as a store of energy. Several growth factors, hormones, and cytokines are secreted by them into the tumor microenvironment. Their primary purpose of producing inflammation and increasing the risk of metastasis is carried out by them secreting adipokines, such as hepatocyte growth factor and leptin. Conversely, overstimulating adipocytes aids in collagen formation and stiffens the microenvironment's structure, (Bożyk *et al.*, 2022).

6. IMMUNE CELLS PRESENT WITHIN THE TUMOR MICROENVIRONMENT OF PROSTATE CANCER:

Tumor-piercing immune cells, including as cytotoxic lymphocytes, tumor-associated macrophages, and myeloid-derived suppressor cells (MDSC), are significant variables that impact the progression of cancer, (Chew, Toh, & Abastado, 2012). As the tumor grows, cancer cells continuously produce a TME that aids in their survival and proliferation, (Pitt *et al.,* 2016). The types of cancer are incredibly diverse, and human tumor tissues can become infiltrated by a wide range of immune cells. The most studied kind of adaptive immune cell is tumor-invading T cells. Numerous T cell phenotypic sub-populations have been described, including CD4+ and CD8+, as well as functional (effector, memory), differentiation (CD4+ T helper 1 (Th1), CD4+ T helper 17 (Th17), and CD4+ Treg) sub-populations. T lymphocytes can influence tumor growth through direct interaction or by stimulating other cells present in the tumor microenvironment, (Cassim & Pouyssegur, 2019). Antitumor responses involve several immune cell lineages. The ability of natural killer (NK) cells to eradicate tumor cells in several cancer models has long been known. Comparably, tumor antigens that are produced in "abnormal" ways on carcinoma cells can be recognized by cytotoxic T lymphocytes, which can then target and kill those cells. Antigen-presenting cells, and dendritic cells in particular, process and present tumor-derived antigens in the context of MHC class I molecules to activate CD8+ T lymphocytes through a process called cross-presentation. In addition to eliminating cancer cells directly, active CD8+ T lymphocytes can also suppress angiogenesis through the release of IFN-γ. Long-term immune surveillance in cancer vaccines involves T- and B-cell memory, B-cell activation, and differentiation into antibody-producing plasma cells, (Chew, Toh, & Abastado,

2012). Due to the extreme variability of malignancies, human tumor tissues may have a broad range of immune cells. The sort of adaptive immune cell that has been studied the most is tumor-invading T cells. Many sub-populations of T cells with various phenotypic characteristics have been described; these include CD4+ and CD8+, as well as functional (effector, memory) and differentiation (CD4+ T helper 1 (Th1), CD4+ T helper 17 (Th17), and CD4+ Treg). T lymphocytes can influence tumor growth through direct interaction or by stimulating other cells present in the tumor microenvironment, (Cassim & Pouyssegur, 2019). Important factors influencing the course of cancer include immune cells that penetrate tumors, such as cytotoxic lymphocytes, tumor-associated macrophages, and myeloid-derived suppressor cells (MDSC). Numerous studies have demonstrated that higher MDSC and TAM density accelerate the growth of tumors through a variety of inhibitory mechanisms, (Chew, Toh, & Abastado, 2012). A complex web of connections between various cell types that together take advantage of metabolic rewiring and mutually alter their functionality is what defines tumor progression. While certain cancer patients have demonstrated exceptional responses to various monoclonal antibody-based therapies, the response rates are still poor and only temporary, (Cassim & Pouyssegur, 2019). On the other hand, cytotoxic lymphocytes in the tumor microenvironment are linked to a favorable outcome in many types of cancer, (Chew, Toh, & Abastado, 2012). Tumor cells can inhibit T-cell chemokine gradients, which play a major role in the extravasation and accumulation of T cells within tumors, (Pitt *et al.,* 2016). The main reason for death from cancer is tumor metastasis. The presence of EMT markers is correlated with a poor prognosis, and the epithelial-to-mesenchymal transition (EMT) of cancer cells is linked to increased cell motility, local invasion, and distant metastasis. Early embryogenesis and the development of cancer share the similar process of EMT. The physical changes that the cancer cells go through during EMT provide them increased mobility and decreased intercellular adhesion, which facilitates local invasion and distant metastasis. Tumor recruitment of MDSC promotes EMT, as demonstrated by our previous study in a spontaneous melanoma model. In particular, we found that granulocytic (G)-MDSC induce EMT in vitro and in vivo via several pathways including TGF-β1, EGF, and hepatocyte growth factor (HGF) (EGF). It has also been demonstrated that other immune cells, such as macrophages and activated CD8+ T cells, induce EMT in tumor-bearing animals. Collectively, these findings highlight the close connection that shapes tumor formation and progression between host immune responses and the microenvironment, (Chew, Toh, & Abastado, 2012). On the other hand, several studies have demonstrated the critical function that chemokines play in metastasis, especially in tumor cells that express the CXCR3 and CXCR4 chemokine receptors.1 Cancer-associated fibroblasts (CAFs) are a predominant component of the tumor stroma and play a major role in the establishment of the TME, with the exception of immune cells, (Yu *et al.,* 2021). Moreover, pro-tumor macrophages are reeducated to an anti-tumor phenotype by enzyme-instructed self-assembly of phosphotyrosine cholesterol, which breaks down macrophage filaments and inhibits the proliferation of ovarian cancer cells.The first class of lipid-based nanoparticles employed in the therapy of cancer are liposomes, (Yu *et al.,* 2021).

CAF:

A significant fraction of the stromal cells in the tumor microenvironment (TME) are cancer-associated fibroblasts (CAFs), which have been demonstrated to produce vital signals that promote tumor growth and enable small subpopulations of cancer cells to elude treatment, (Labani-Motlagh, Ashja-Mahdavi, & Loskog, 2020). In cases of pancreatic, lung, and breast cancer, a higher number of CAFs in the tumor stroma has been linked to a worse clinical prognosis, (Wu & Dai, 2017). Dysregulated fibroblasts known

as CAFs are produced when tumor stromal cells differentiate. They play a role in immune-surveillance evasion and extracellular matrix (ECM) remodeling. Being the most abundant cell population of non-cancerous components in the TME of solid tumors, CAFs play a major role in the formation of immunosuppressive TME and tumor growth. Tumor-promoting inflammation is aided by CAFs by drawing immune cells to the TME via cytokine and chemokine secretion. Known to promote macrophage infiltration, ease the transition of macrophages to the M2 immunosuppressive phenotype, and limit the recruitment of cytotoxic CD8+ T lymphocytes into the breast tumor microenvironment, chictinase-like protein 3 (Chi3L1) is released by CAFs. The expression of fibroblast activation protein (FAP) on the surface of CAF promotes the recruitment of type M2 macrophages, MDSCs, and Tregs into the liver tumor bed as well as the switch from Th1 to Th2 immunity, (Cortellino & Longo, 2023). The majority of activated CAFs are derived from resident fibroblasts, which are recruited and activated by a variety of growth factors and cytokines prevalent in the TME, such as PDGF, FGF2, and TGFβ. CAFs can also be generated from bone marrow-derived mesenchymal stem cells or from endothelial or epithelial cells that are localized in the tumor stroma through the processes of epithelial-mesenchymal transition (EMT) or endothelial-mesenchymal transition (EMT), (Wu & Dai, 2017). In summary, lysophosphatidylcholine, which is required for the creation of cell membranes, and lysophosphatidic acid, a biomolecule with growth factor-like characteristics, are produced by CAFs and contribute to the growth of pancreatic tumors. They also leave behind collagen, which pancreatic cancer cells use to break down and create proline, which is necessary to keep the tricarboxylic acid (TCA) cycle going, (Cortellino & Longo, 2023).

NK cells:

Natural killer (NK) cells are a crucial part of anti-cancer effector cells. They offer great potential for immunotherapy, despite the fact that diminished functioning during cancer limits their potency. After activation, NK cells increase aerobic glycolysis. Elevated IL-15 stimulation induces NK cells to express more of the amino acid transporter chaperon CD98 and transferrin receptor CD71. It also increases mTOR activity and glucose uptake in support of bioenergetic metabolism. It has been demonstrated that this procedure is necessary to maintain NK cell proliferation throughout development and the acquisition of cytolytic capacity. Consequently, decreased cytotoxic activity in NK cells is caused by impairment of glucose metabolism and disruption of mTOR signalling. Are center port demonstrated that by boosting both glycolysis and OXPHOS, sterol regulatory element binding protein (Srebp) transcription factors contribute significantly to the cytokine-induced metabolic reprogramming of NK cells. Moreover, Srebp suppression reduced the cytotoxicity of NK cells and stopped this phenotype. It is still unknown, nevertheless, whether metabolic changes discovered in malignancies may have an impact on Srebp-mediated NK cell function and metabolic activity, (Wu & Dai, 2017). Furthermore, it is believed that DCs and NK cells contribute to a strong anti-tumor immune response; nevertheless, a variety of immunosuppressive conditions often limit their potential and cause them to adopt pro-tumor phenotypes, (Pitt *et al*., 2016). In some cancers, a pro-inflammatory phenotype coupled with cytotoxic lymphocyte infiltration of the tumor is linked to a better prognosis. T cell-mediated tumor infiltration has been associated with improved prognoses in lung, colorectal, breast, ovarian, and melanoma cancers. There is a strong association between a good prognosis and the densities and distribution of T and B lymphocytes, according to recent studies on breast and liver malignancies. Our research in HCC found a relationship between higher patient survival with T and NK cell intratumor concentrations, (Chew, Toh, & Abastado, 2012). The findings of Coley are justified by the expanding body of information on

tumor immunology. While infiltrating immune cells such as DCs, NK cells, and CTLs are suppressed in response to tumor-mediated factors, other cell types like myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs) are utilized by the tumor to its benefit, (Van der Jeught *et al.,* 2015).

7. HOST IMMUNE RESPONSE TO TUMORS:

Tumor recognition as foreign matter and tumor access for immune effector cell destruction are prerequisites for a successful host immune response, (Cassim & Pouyssegur, 2019). Although the host immune system's efficient tumor surveillance guards against illness, persistent inflammation and tumor "immunoediting" have also been linked to the onset and progression of disease. Consequently, a positive prognosis for cancer patients is co-related with the reactivation and maintenance of adequate antitumor responses inside the tumor microenvironment, (Chew, Toh, & Abastado, 2012). During surveillance, the host immune system may identify changed protein products produced by many mutations in unstable tumor genomes as foreign, (Cassim & Pouyssegur, 2019). One significant factor influencing the tumor microenvironment is the immune system. In fact, during the past few decades, a great deal of research has been done on the intricate interactions that exist between cancer cells and the host immune system, (Chew, Toh, & Abastado, 2012). The TME contains a range of cell types that concentrate at various phases of tumor growth. Hematopoietic and endothelial progenitor cells produced from bone marrow, infiltrating immune cells, and carcinoma-associated fibroblasts are some of the main cell types that enter tumors in their early stages of development. Tumor control depends on immune cells such dendritic cells (DCs), macrophages, lymphocytes, and natural killer (NK) cells incorporating cancers early on. However, the activity of immunosuppressive cells, such as type 2-polarized macrophages (M2), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSC), which are inherently linked to the growing TME, inhibits the anticancer immune response produced by these cells, (Pitt *et al.,* 2016).

8. TARGETING THE TUMOR MICROENVIRONMENT WITH THERAPIES:

Tumors that enable T cell trafficking and immune cell infiltration may use immunosuppressive mechanisms to avoid host response. Immunological checkpoints, part of peripheral tolerance, play a crucial role in immunological evasion by protecting against autoimmunity. T cells receive the self-antigenic molecules that APCs have picked up either in the absence of co-inhibitory signals, like PD-1 binding to PD-L1, or in the presence of appropriate co-activation signals, like CD80 or CD86 to CD28, (Hendry *et al.,* 2016). Tumor therapies often comprise chemotherapy, radiation, and immunotherapy. Targeting macrophages during tumor treatment can create synergistic benefits by changing their behavior, (Xu *et al*., 2022). Previously, It was believed that radiation therapy (RT) would create an immunosuppressive microenvironment. RT activates the ATM protein pathway, which includes P53 and NF-κB transcription factors. Radiation can activate NF-κB without DNA damage by activating TNFR-associated factors (TRAFs). NF-κB regulates the expression of pro-inflammatory immune response molecules such as TNF-α, IL-1, CCL5, adhesion molecules like ICAM-1, E-selectin, and VCAM-1, as well as MHC molecules, and anti-apoptotic genes like Bax and Bcl-2, (Shiao & Coussens, 2010). Cytotoxic medicines, such as chemotherapy and radiation therapy, cause cells to release ATP rapidly. ATP activates

the NLRP3-dependent caspase-1 activation complex, also known as the inflammasome, by binding to the P2X purinergic receptor on DCs. Inflammasome activation triggers the release of pro-inflammatory cytokines including IL-1β, which are crucial for priming T cells. When components of this system (NLRP3, caspase-1, or IL-1R) are lacking, T cell responses to cells destroyed by chemotherapy or radiotherapy are diminished, demonstrating that ATP release from dying cells is an important part of immunogenic cell death and anti-tumor immunity, (Shiao & Coussens, 2010). In treating cancers there are several other ways to characterize the TME, we can use several other new treatments like small molecular weight drugs, antibody-based agents, and transduced lymphocytes these techniques can be used to improve the results in the treatment of cancer patients, (Shiao & Coussens, 2010). Immunotherapeutic approaches have changed the course of treatment and prognosis for a few solid cancers, such as non-small cell lung cancer (NSCLC) and melanoma. Still, they are ineffective and have not produced long-term responses for the great majority of cancer patients. Antibodies with monoclonal structure designed to target the inhibitory proteins CTL antigen 4 (CTLA-4) or programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) on T cells or cancer cells are used in ICB immunotherapy to stimulate the immune response. But response rates are still very different, and it's still hard to find good indicators of ICB responsiveness. It has been claimed that PD-L1 expression, high tumor mutational burden (TMB), which is significantly impacted by the epitopes shown in a tumor's human leukocyte antigen (HLA) genes, and the presence of CD8+ T cells are predictive of clinical response to ICB treatment. CD8+ T cells are solidly established as the ultimate effectors of tumor rejection and the best predictor of ICB response across tumor types. The functional diversity of tumor-infiltrating T lymphocytes significantly impacts their cytotoxicity. Reactivation of dysfunctional CD8+, memory-like CD8+TCF7+, CD103+ tumor-resident CD8+, and Tcf1+PD-1+ CD8+ T cells with stem-like features resulted in long-lasting responses. CD4+ T cell subpopulations play a critical role in immunotherapy, including CD4+ Th1 cells that generate functional CD8+ T cell responses, CD4+FoxP3+ regulatory T cells (Treg), which suppress antitumor immune responses in several cancers, though responses to CTLA-4 blockade have been shown, and CD4+FoxP3−PD-1Hi (4PD-1Hi). Persistent T cells following PD-1 inhibition can signal a bad prognosis, (Benavente *et al*., 2020).

Clinical anticancer treatment efficacy is hampered by various reasons, including tumor heterogeneity and cancer cells' potential to develop multidrug resistance. The interaction between tumor cells, stromal cells, and other TME components complicates effective treatment. We can target the TME in the treatment of cancer by targeting the CAFs, ECs, IICs, microbiomes, (Naser *et al*., 2022). In TME, the immune system has a significant impact on tumor responses to various treatment regimens. As a result, several techniques based on attacking the immune system have been utilized to combat cancer: (i) reducing macrophage recruitment to tumor tissues; (ii) blocking macrophage differentiation toward TAMs; and (iii) increasing the immune system's anti-tumor action. Several studies show that combining conventional medicines with immunotherapy produces excellent clinical results. Indeed, the combination of chemotherapy medicines and immune checkpoint inhibitors (ICIs) has shown greater results than chemotherapy alone, (Wu *et al.,* 2021).

In situ proliferation during tumor growth contributes to the expansion of this resident macrophage pool, which is further enhanced by the migration of monocyte-derived macrophages (MDM) into the TME. Consequently, a mosaic of ontogenically distinct TAMs is generated, which are subsequently refined or modified within the TME. This leads to significant phenotypic and functional heterogeneity across a variety of tumor types, such as lung, breast, pancreatic, and brain malignancies. Within the TME, TAMs are polarized to adopt a variety of phenotypes spanning from proinflammatory to anti-inflammatory

states. They can respond quickly to local stimuli, such as cytokines or therapeutic perturbations, (Bejarano, Jordão, & Joyce, 2021).

Inhibitors of CSF1R. For macrophage differentiation and survival, the transmembrane tyrosine kinase class III receptor CSF1R is necessary. The binding of CSF1 and IL34, two of its ligands, initiates CSF1R signalling. Certain tissues, like the liver, skin, and brain, have different patterns both in space and time. While elevated serum levels of CSF1 are frequently linked to poor patient outcomes, such as in the case of ovarian and endometrial cancers, the function of IL34 in cancer has not received as much attention. This is partly because it was only recently discovered to be a substitute ligand for CSF1R and has a more restricted expression pattern than CSF1, (Bejarano, Jordão, & Joyce, 2021).

CCL2/CCR2 Blockers. One of the main reasons for the increase in TAMs in the TME is the synthesis of chemokines, which lead to the recruitment of monocytes, the accumulation of MDM within the tumor, and the expansion of the tissue-resident macrophage pool. Cancer cells produce CCL2, which draws tissue-resident macrophages that extravasate into tumor sites and mature into TAMs, as well as CCR2-expressing Ly6Chi monocytes from the systemic circulation. Prostate and breast cancers are among the many tumor types for which high CCL2 levels in the serum and TME are frequently linked to a poor prognosis. In mouse models of these cancers, it was found that blocking CCL2 with neutralizing antibodies sequestered Ly6Chi monocytes in the bone marrow, preventing TAM accumulation and enhancing CD8+ T cell antitumor efficacy in the TME, which in turn led to decreased tumor growth and metastasis, (Bejarano, Jordão, & Joyce, 2021).

Many of the drugs used to target TAMs may also affect other APC subsets, which could have larger effects because innate immune cells can respond to common environmental signals during disease and can share comparable cell-surface receptor repertoires. TAMs and DCs are examples of APCs that express CD40, a member of the TNF receptor superfamily that is crucial to the activation and proliferation of these cells. CD40 is a crucial modulator of T cell-dependent antitumor immunity via its interaction with CD40 ligand (CD40L), which is mostly produced by CD4+ T cells. Activating the CD40–CD40L axis results in the upregulation of MHC molecules and the production of proinflammatory cytokines, including IL12, which are crucial for T-cell priming, (Bejarano, Jordão, & Joyce, 2021).

They are emerging in TAM. Other approaches that seek to rewire TAMs are also being evaluated in early clinical stages. PI3K and TREM2 inhibition is one of these. Due to its significance in controlling angiogenesis, growth, motility, survival, metabolism, and other processes in cells, the PI3K signalling pathway has been the subject of numerous therapeutic trials, mostly to directly target cancer cells. Members of the PI3K family also have significant effects on the immune system. One important regulator of TAM-mediated immunosuppression, for instance, is PI3Kγ. In animal models, TAMs with selective PI3Kγ inactivation expressed more MHC-II and IL12 and less IL10, which attracted immune cells with antitumoral potential and caused tumor regression, (Bejarano, Jordão, & Joyce, 2021).

CONCLUSION

The development, course, and response to treatment of cancer are all significantly influenced by the tumor microenvironment (TME). It is made up of several cell components that interact with tumor cells in a dynamic way, such as blood vessels, fibroblasts, immune cells, and inflammatory cells. Through the creation of an immunosuppressive environment that impedes the effectiveness of anti-tumor immune responses, these interactions can promote tumor development and metastasis. The goal of cancer im-

munotherapy is to use the immune system to locate and destroy cancer cells, however its effectiveness varies depending on the kind of cancer, especially prostate cancer (PCa), where T-cell shortages are a major obstacle to treatment. Immune checkpoint blockade (ICB) is critical for regulating the tumor microenvironment (TME) and boosting anti-tumor immunity, according to recent studies. Treatment difficulties arise from the intricate interactions between tumor cells and their surroundings, though, since immune evasion strategies and hypoxia can both impair T-cell activity. Comprehending the makeup and dynamics of the tumor microenvironment (TME) is crucial to the development of more potent therapeutic approaches that target the environment as well as tumor biology, potentially improving outcomes for patients with different types of cancer.

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