Review Article

Unmasking Cancer's Nemesis: The Immune System's Role in Tumorigenesis

Puja Bharti*, U Rajashekhar, Mehdi Fathima, Saroj Kumar Sah
Department of Pharmacology, Karnataka College of Pharmacy, Bangalore-560064, Karnataka, India.
***Corresponding author's E-mail:** pujabharti24700@gmail.com

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ABSTRACT

The immune system plays a pivotal role in cancer advancement by engaging with tumor cells and influencing their development. Various factors such as T-cell reactions, patterns of immune cell infiltration, and immune dysregulation impact the tumor microenvironment and cancer progression. The immune system is consistently vigilant for abnormal cells and eliminates them through immune surveillance. Specialized cells like dendritic cells recognize and present tumor antigens to T cells, which coordinate the targeted elimination of cancerous cells. However, cancer cells employ diverse strategies to evade immune detection and control. They may express molecules that hinder T cell function, such as PD-L1, or establish an immunosuppressive tumor microenvironment characterized by regulatory T cells and immunosuppressive cytokines. These mechanisms enable tumors to proliferate unchecked. Comprehending the intricate interplay between the immune system and cancer is critical for devising effective therapeutic approaches. Immunotherapy exploits the immune system's capabilities to combat cancer. By obstructing immune checkpoints or enhancing immune cell activity, these treatments seek to reinvigorate the body's innate tumour-suppressive reaction.

Keywords: Immune system, Cancer, Dendritic cells, Tumour microenvironment, T- cells.

INTRODUCTION

Immunotherapy has revolutionized cancer treatment by targeting tumor-specific antigens and down-regulating immune checkpoint proteins to increase anti-tumor immunity [1]. However, the efficacy of immunotherapy remains constrained in many clinical environments; indicating the need for a better understanding of tumor immunology [2]. Cancer is a condition that impacts the entire immune system, causing alterations in both the tumor microenvironment (TME) and the peripheral immune system. [3] The peripheral immune system performs a crucial role in driving effective natural and therapeutically induced anti-tumor immune responses [4]. Innate immunity, including innate immune cells in the TME, has been shown to influence the clinical outcomes of tumor patients and holds potential for the development of new immunotherapies [5]. Nevertheless, obstacles persist in effectively stimulating innate immune responses and improving anti-tumor efficacy. Understanding and controlling factors such as tumor-borne adenosine, lactate, and hypoxia can significantly affect the effectiveness of restoring and sustaining immunity in individuals with cancer.

The immune system serves a vital function in defending the body against detrimental pathogens and external agents. It comprises an intricate network of cells, tissues, and organs working together to protect the body from infections, illnesses, and various potential hazards. [6] When the body is invaded by a pathogen like a bacteria or virus, the body's immune system perceives it as foreign and initiates an immune response. This response includes various mechanisms to eliminate the pathogen, such as the production of antibodies, activation of specific immune cells, and release of inflammatory molecules.

Immunity can be classified into two main types:

Innate immunity: Serving as the primary defense mechanism, innate immunity is inherent from birth. It includes protective structures such as the skin and mucous membranes, alongside immune defenders like neutrophils, natural killer cells, and macrophages. [7]

Adaptive immunity: Conversely, adaptive immunity is a targeted immune response that evolves gradually following exposure to a particular pathogen. Adaptive immunity involves the triggering of specialized immune cells called B cells and T cells, which have the capacity to recognize and remember specific pathogens. These immune cells, once activated, can produce antibodies to neutralize pathogens and also coordinate the immune response to eliminate the threat. [8]

In contrast, cancer is a multi-dimensional and intricate condition marked by the unregulated proliferation and division of abnormal cells within the body. (6) Cancer can arise from various factors, including genetic mutations, exposure to carcinogens, disruptions in normal cellular processes. [9,10,11]

The immune system's involvement in cancer development is pivotal. Equipped with mechanisms to identify and eradicate abnormal cells, including cancerous ones, it serves as a frontline defense. Nevertheless, cancer cells frequently devise strategies to escape immune detection, allowing unchecked proliferation and growth. This can transpire through diverse mechanisms, such as diminishing immune cell activation, generating immunosuppressive molecules, or modifying the expression of antigens recognized by body's immune system. The role of the immune system in cancer is intricate. It assumes a dual function: either both suppressing tumor growth and

facilitating tumor elimination, or conversely, aiding tumor progression and evasion. When the immune system identifies cancer cells as aberrant, it can mount an immune response to target and eliminate them. This response includes various mechanisms to eliminate the pathogen, such as the generation of antibodies, activation of specific immune cells, and release of inflammatory molecules. In some cases, the immune response is successful in preventing or controlling cancer growth. [12]

However, cancer cells possess the capability to circumvent and dampen the immune response. They can do this by producing immunosuppressive molecules that inhibit the function of immune cells or by altering their own antigens to become less recognizable to the immune system. Furthermore, neoplastic cells can exploit the normal regulatory mechanisms of the immune system to escape detection. For example, they can upregulate immune checkpoints, which are proteins on the surface of immune cells that regulate the magnitude and longevity of an immune response. [13] When these immune checkpoints are activated, they can dampen the immune response and prevent it from effectively targeting and eliminating cancer cells.

Immune Surveillance and Immuno editing:

Immune surveillance:

Immune surveillance is a vital function whereby the immune system actively monitors the body to recognize and eradicate abnormal cells, including those that may be cancerous or precancerous, prior to their development into tumors. [14] The process of immune surveillance involves the detection and elimination of abnormal cells, including cancer cells, before they have the opportunity to form tumors. Initially proposed by Paul Ehrlich in 1909, this concept was further developed by Lewis Thomas and Sir Frank Macfarlane Burnet. [15, 16]

Paul Ehrlich first introduced the theory of immune surveillance in 1909, postulating that the immune system could potentially hinder tumor development by eliminating abnormal cells. This notion was expanded upon in the 1950s by Lewis Thomas and Frank Macfarlane Burnet, who postulated that the immune system recognizes and removes nascent tumor cells displaying distinctive antigens. [16]

Experimental evidence bolstering the immune surveillance theory encompasses findings demonstrating that mice with compromised immune systems exhibit a heightened susceptibility to cancer compared to their immunocompetent counterparts. Furthermore, observations in immunosuppressed patients reveal an increased prevalence of specific cancers. [16, 17]

Recent literature underscores the pivotal role of immune surveillance in cancer prevention by emphasizing the ability of immune system to recognize and eradicate abnormal cells, including cancerous ones, prior to tumor formation. Research indicates that immune surveillance significantly contributes to suppressing cancer in humans, as evidenced by the elevated cancer risk among immune deficient individuals, such as transplant recipients undergoing immunosuppression. Despite mounting evidence supporting the relevance of immune surveillance in cancer etiology and treatment, its significance remains a subject of debate, particularly among non-immunologists and oncologists who frequently prioritize cell-intrinsic factors. [15, 16, 17]

Immuno editing:

The concept of Immuno editing, characterized by a dynamic sequence of elimination, equilibrium, and escape, elucidates the intricate engagements between the immune system and tumors. Initially, this process involves the immune system identifying and eliminating abnormal cells during the elimination phase. However, it can subsequently lead to opting for less immunogenic tumor variants that dodge immune detection during the equilibrium and escape phases. Moreover, comprehending the interplay between cell-extrinsic (immune-mediated) and cell-intrinsic mechanisms is essential for discerning both tumor suppression and development. [18]

Immunoediting stands as a captivating concept elucidating the dynamic interplay between the immune system and emerging tumors. It encapsulates a multi-stage progression wherein the immune system perpetually engages with and shapes the evolution of a tumor.[19] This complex dance can have both beneficial and detrimental effects on cancer progression.

The Immunoediting process is generally divided into three phases:

Elimination: In the initial phase, a vigilant immune system identifies and eliminates early tumor cells containing immunogenic markers. This scenario ideally prevents the emergence of clinically detectable cancer.

Equilibrium: If complete elimination proves unsuccessful, the immune system may enter a state of equilibrium with the tumor. This can entail the emergence of tumor variants with diminished immunogenicity, enabling their persistence while exhibiting slow growth.

Escape: Over time, tumor cells can acquire mechanisms to evade immune recognition and control, facilitated by ongoing mutations and immune pressure. This escape phase permits the proliferation of aggressive and clinically consequential tumors. [20]

Immune Evasion Mechanisms

Strategies employed by tumour cells to avoid immune detection and destruction

Cancer progression is characterized by the development of numerous hallmarks, one of which is the ability to evade immune spotting and eradication. This immune evasion allows cancer cells to proliferate and disseminate throughout the body unchecked. Cancer cells achieve this

by employing a multifaceted arsenal of strategies, including:

1. Downregulation of MHC-I and Antigen Presentation

Major histocompatibility complex class I (MHC-I) molecules are crucial for antigen presentation to cytotoxic T lymphocytes (CTLs). Cancer cells can downregulate MHC-I expression or even completely lose MHC-I molecules on their cell surface. This impairs their recognition by CTLs, rendering them invisible to the immune system's targeted attack. Additionally, cancerous cells can downregulate the expression of antigens themselves, further hindering immune recognition. [21,22]

2. Tumor-Specific MHC-I Loss: A Threat to Immune Recognition and Survival

The capacity of cancer cells to avoid immune detection poses a significant hurdle in cancer therapy. One critical mechanism for this evasion is the loss of tumor-specific Major Histocompatibility Complex Class I (MHC-I) expression.23, MHC-I molecules act like flags on a cell's surface, displaying fragments of proteins made within the cell. This allows the immune system, particularly cytotoxic T cells (CTLs), to detect and eliminate abnormal cells, including cancer cells. [23, 24]

Unfortunately, tumors may downregulate or entirely abolish MHC-I expression, rendering them imperceptible to CTLs. This loss of tumor-specific MHC-I is linked to worse prognoses in cancer patients, including shorter survival times and increased metastasis, the spread of cancer to other organs.[23,24,25]

There are three main culprits behind this MHC-I loss:

Genetic Alterations: Mutations or deletions in genes responsible for MHC-I production can occur within the tumor itself. This directly disrupts the machinery needed to display these molecules on the cell surface.[23,26]

Antigen Depletion: Tumors may strategically deplete the proteins that are normally presented by MHC-I. This deprives CTLs of their "targets" on the tumor cell, hindering recognition and attack.[27]

Transcriptional Modulation: Regulatory mechanisms within the tumor cell can be manipulated to switch off MHC-I gene expression. This effectively silences the "flag-waving" system, allowing the tumor to escape immune scrutiny.28

By employing these strategies, tumors create a cloak of invisibility, making them difficult for the immune system to identify and eliminate. This highlights the importance of developing strategies to:

Restore MHC-I Expression: Treatments capable of restoring MHC-I loss in tumors might stimulate the immune system to identify and eradicate cancer cells. [23,25]

Target Alternative Pathways: Therapies that exploit alternative immune recognition mechanisms, independent of MHC-I presentation, could offer new avenues for attacking tumors that have lost MHC-I expression.[25]

Understanding the role of tumor-specific MHC-I loss is crucial for developing effective cancer immunotherapies. By overcoming this immune evasion tactic, we can improve the capability of the immune system to fight cancer and potentially improve patient outcomes.

3. Immune Checkpoint Molecule Expression

Immune checkpoint molecules act as critical regulators of the immune response, playing a pivotal role in averting exaggerated immune activation and maintaining self-tolerance. However, within the context of cancer, their expression enables tumors to evade immune recognition and destruction. Recent research has provided insight into the complexities of immune checkpoint molecule expression in cancer, providing valuable insights for therapeutic development.

1. Co-expression and Interplay: Studies have identified the co-expression of multiple checkpoint molecules, such as PD-1, CTLA-4, LAG-3 and TIM-3, on tumor-specific T cells . This co-expression suggests a complex interplay between these molecules in regulating the immune system's response within the tumor microenvironment.

2. Signaling Pathways and Combinatorial Blockade: While the precise signaling cascades associated with each checkpoint molecule remain under investigation, therapeutic strategies targeting multiple checkpoints simultaneously have shown promise. Pre-clinical cancer models and studies on chronic viral infections demonstrate improved outcomes with combined blockade using specific monoclonal antibodies. [29] Clinical data further strengthens this approach, with encouraging results observed in patients diagnosed with metastatic melanoma who underwent combined checkpoint blockade therapy. [29]

3. Immune Evasion and Tumor Tolerance: PD-1, in particular, seems to play a central role in establishing tumor tolerance. The frequent observation of PD-1 expression on tumor-infiltrating lymphocytes (TILs) across various cancers suggests its involvement in immune evasion 29. The upregulation of PD-1 within a tolerogenic tumor microenvironment further underscores its contribution to tumor immune escape [30]

4. Co-expression Patterns and Therapeutic Strategies: Pre-clinical models and studies of human diseases reveal the co-expression of multiple checkpoint molecules on CD4+ and CD8+ T cells, with PD-1 frequently co-expressed with others. [29] Understanding these co-expression patterns is critical for designing effective combination therapies that target multiple inhibitory pathways simultaneously.

5. Clinical Implications and Personalized Medicine: The success of combined checkpoint blockade in treating melanoma patients highlights its clinical potential. [31, 32] However, more investigation is needed to elucidate the long-term efficacy of this approach and its applicability

across diverse cancer types. Personalized medicine strategies may ultimately be required to maximize the effectiveness of combination checkpoint blockade therapies, tailoring treatment regimens to the specific immune checkpoint landscape of each patient's tumor. the intricate interplay between immune checkpoint molecules paints a complex picture of immune regulation in cancer. Exploring the co-expression patterns and their role in immune evasion paves the way for developing novel therapeutic strategies.

4. Antigen Masking by Glycosylation: A Shielding Tactic Employed by Tumors

Cancer cells possess a diverse arsenal of mechanisms to evade immune detection and destruction. One such strategy involves antigen masking by glycosylation, a process that utilizes carbohydrates to cloak tumor-associated antigens, hindering their recognition by the immune system.

The Glycosylation Process:

Cells naturally decorate proteins and lipids with sugar molecules (glycans) in a process called glycosylation. This modification plays various roles in cellular function, including protein folding, stability, and cell-cell interactions. However, cancer cells can exploit this process for their advantage.

Antigen Camouflage:

Cancer cells can upregulate the addition of specific glycans, particularly sialic acid, to their surface antigens. This creates a dense sugar coat, or glycocalyx, that acts as a camouflage, obscuring the underlying antigens from immune recognition. These masked antigens become invisible to immune cells, particularly T lymphocytes and antigen-presenting cells (APCs) like dendritic cells.

Reduced Antigen Binding:

The bulky glycan coat can sterically hinder the binding of antibodies and T cell receptors (TCRs) to their cognate antigens on the tumor cell surface [33,34]. This directly hampers the immune system's capacity to identify and target the tumour cells.

Impaired Antigen Presentation:

Glycosylation can also affect how APCs process and exhibit tumor antigens to T cells. The glycan modifications may interfere with antigen processing within the APC or mask crucial epitopes (antigen fragments) required for TCR recognition [35].

Consequences for Cancer Progression:

Antigen masking by glycosylation contributes to immune evasion and tumor progression in several ways:

Reduced T cell Activation:

By preventing proper antigen recognition, glycosylation can hinder T cell activation and the generation of an effective cytotoxic T lymphocyte (CTL) response against the tumor [35].

Suppressed Antibody Production:

The masking of antigens can also limit the capability of B cells to produce antibodies that can effectively target and eliminate cancer cells.

Therapeutic Implications:

Understanding the role of antigen masking by glycosylation is crucial for developing novel cancer immunotherapies. Strategies to overcome this immune evasion tactic include:

Unmasking Glycans:

Enzymes that cleave specific glycans (glycanase) could potentially be used to remove the sugar coat from tumor cells, exposing hidden antigens to immune recognition 36.

Targeting Glycan Biosynthesis:

Drugs that inhibit the enzymes responsible for attaching glycans to tumor antigens may be used to prevent the formation of the glycocalyx and enhance immune recognition [36].

Glyco-mimicry Vaccines:

Vaccines designed to elicit antibodies against specific tumor-associated glycans could potentially target and eliminate cancer cells masked by these sugars [36].

Recruitment of Immunosuppressive Cells in Cancer: A Devious Strategy for Tumor Escape

Cancer progression is not solely driven by uncontrolled cell proliferation. Tumors actively manipulate the immune system to create a tolerogenic microenvironment, fostering their growth and survival. A key strategy in this immune evasion arsenal is the recruitment of immunosuppressive cells, populations that actively suppress the anti-tumor immune response. Understanding the mechanisms of this recruitment is crucial for developing novel cancer immunotherapies.

Cellular Cast of Characters: Several immunosuppressive cell types are recruited to the TME through a complex interplay of chemokines, cytokines, and adhesion molecules. Key players include:

Myeloid-Derived Suppressor Cells (MDSCs):

A varied group of immature myeloid cells exhibiting powerful immunosuppressive capabilities. MDSCs hinder T cell activation and proliferation via diverse mechanisms; including the depletion of L-arginine, production of reactive oxygen species (ROS), and expression of inhibitory molecules like PD-L1 [37].

Regulatory T cells (Tregs):

A specific subset of CD4+ T cells that dampen immune responses. Tregs can directly suppress the effector T cell

function through cell-cell contact and cytokine secretion, hindering their anti-tumor activity [38].

Tumor-Associated Macrophages (TAMs):

Macrophages have the capacity to polarize into two primary phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory). TAMs within the TME are predominantly of the M2 phenotype and contribute to the suppression of the immune system by secreting factors that inhibit T cell activation and promote tumor growth [39].

Orchestrating the Recruitment:

Tumor cells and stromal cells within the TME orchestrate the recruitment of immunosuppressive cells through the following mechanisms:

Chemokine Signalling:

Tumors secrete various chemokines, like CCL5, CCL2, and CXCL12 that bind to specific receptors on immunosuppressive cells, directing their migration towards the TME [40].

Cytokine Production:

Tumor-derived cytokines, like IL-10 and TGF-β, promote the expansion and activation of immunosuppressive cells within the TME[41].

Adhesion Molecule Expression:

Adhesion molecules expressed by tumor and stromal cells facilitate the attachment and infiltration of immunosuppressive cells into the TME [40,41]

Consequences of Recruitment:

The influx of immunosuppressive cells within the TME has a profound impact on the anti-tumor immune response:

Suppressed T cell Activity: Immunosuppressive cells directly inhibit the activation, proliferation, and cytotoxic function of effector T cells, hindering their ability to eliminate cancer cells [42].

Immune Tolerance Induction: Regulatory T cells promote immune tolerance within the TME, preventing the immune system from identifying the tumor as foreign [43].

Angiogenesis Promotion: Immunosuppressive cells can promote tumor angiogenesis, the formation of new blood vessels, by secreting factors that stimulate endothelial cell growth, further facilitating tumor expansion and metastasis [42,44].

Therapeutic Implications:

Targeting the recruitment of immunosuppressive cells holds promise for improving cancer immunotherapy:

Chemokine Receptor Blockade: Antibodies or small molecules that block chemokine receptors on immunosuppressive cells can prevent their migration to the TME [40].

Depleting Immunosuppressive Cells: Tactics for diminishing immunosuppressive cell populations within the TME, like employing specific antibodies or targeted therapies, might amplify the anti-tumor immune reaction.[42].

Reprogramming the TME: Therapies aimed at reprogramming TAMs from an immunosuppressive M2 phenotype to a pro-inflammatory M1 phenotype could promote anti-tumor immunity [39].

Tumor Microenvironment and Immunosuppression

The Tumor Microenvironment:

The vicinity of a tumor, called the tumor microenvironment (TME), is a crucial battleground where the immune system fights to control cancer cell growth. [45] This intricate environment is made up of different cell types and molecules, some working to fight the tumor and others helping it grow.[46]

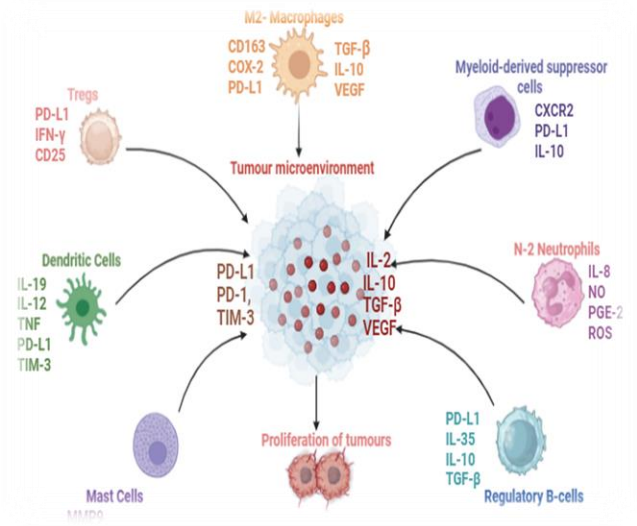

Figure 1: Tumour Microenvironment and Immunosuppression

The Immune System's Arsenal:

Lymphocytes: These soldier cells include CD8+ T cells (cytotoxic T cells), natural killer (NK) cells, and CD4+ helper T cells. They work together with pro-inflammatory macrophages (M1) and dendritic cells to launch an anti-tumor immune response.

Dendritic Cells: These act as generals, directing the immune system's attack by presenting tumor antigens (flags) to T cells, triggering their activation.[45]

The Tumor's Immune Evasion Strategies:

Myeloid-Derived Suppressor Cells (MDSCs) and Regulatory T cells (Tregs): These immunosuppressive cells act like traitors, dampening the immune response and protecting the tumor. Tumors attract and expand these populations to weaken the attack[45,46]. Tumors employ various strategies to evade immune detection and destruction. Tumors may downplay or lose their antigens, making them invisible to T cells. Tumors release

immunosuppressive molecules like IL-10 and TGF-β, creating a tolerogenic environment that hinders immune attack. Tumors can shed MHC-I molecules, essential for antigen presentation, and lose adhesion molecules, making them less susceptible to immune cell attachment. Tumors may upregulate anti-apoptosis proteins like BCL-2, making them harder to kill. Tumors can overexpress PD-L1, a molecule that attaches to a receptor on T cells, essentially putting the brakes on their attack. [47]

The Overall Impact

Tumor-released molecules significantly shape the TME, creating an immunosuppressive environment that weakens the immune response. This allows the tumor to grow and evade elimination. While T cells play a central role, other immune cells contribute to the fight:

M1 Macrophages: These directly attack tumors by releasing toxins and inflammatory molecules.[45],

Basophils: They attract CD8+ T cells to the tumor site.[46]

Eosinophils: These can directly kill tumor cells and activate T cells.

Neutrophils (N1 type): They can activate T cells, induce tumor cell death, and participate in antibody-dependent cell-mediated cytotoxicity (ADCC).

Comprehending the complicated interplay within the TME is crucial for developing effective cancer therapies. By targeting immunosuppressive tactics and bolstering the immune system's attack, we can improve the body's ability to fight cancer. [47,48,49,50.]

Tumor-Infiltrating Lymphocytes (TILs):

Tumor-infiltrating lymphocytes (TILs) constitute a diverse assortment of lymphocytes that invade the tumor locale following specific molecular signals. This infiltration encompasses a range of T cell subsets, including effector T cells, regulatory T cells (Tregs), and the innate lymphoid cells (ILCs) like natural killer (NK) cells and natural killer T (NKT) cells.

Recruitment and Extravasation:

Effector T cells and NK cells are often enlisted into the TME to eradicate cancer cells. This mobilization is facilitated by a complex interplay of adhesion molecules and chemokines. Integrins, Selectins and chemokines produced by tumor cells and the surrounding stroma regulate the infiltration of immune cells, ultimately influencing tumor cell multiplication and dissemination. [23] For instance, CXCL16 and its receptor CXCR6 are known to increase the infiltration of CD8+ and CD4+ T cells in colorectal cancer [24]. Conversely, CCL22 mediates the accumulation of immunosuppressive Tregs within the TME, as observed in breast and ovarian cancers [25]

Despite the presence of TILs within the TME, their ability to effectively penetrate the tumor parenchyma is often hampered. Dysregulated vasculature within tumors can downregulate receptors crucial for TIL attachment, rolling, and transmigration, significantly limiting their infiltration depth. Additionally, the chemokine profile within the TME can be actively manipulated by M2 macrophages and other immunosuppressive cells. These cells can secrete factors that attract further immunosuppressive cell populations while simultaneously hindering TIL infiltration [26.]

Prognostic Significance of TILs

The presence and composition of TILs hold significant prognostic value in cancer patients. Research has indicated that a high concentration of CD3+, CD4+, and CD8+ TILs correlates with enhanced overall survival rates.[27] Conversely, high levels of FoxP3+ Tregs within the TIL population correlate with a negative prognosis [28]. These findings emphasize the heterogeneity of TILs and emphasize the importance of understanding both the anti-tumor and tumor-supportive TIL subsets within the TME.

Composition and function of the tumor microenvironment

The tumor microenvironment (TME) represents an intricate and ever-changing entity pivotal in cancer's evolution, advancement, and therapeutic approaches. It consists of an array of cellular and non-cellular elements interacting with both one another and malignant cells, thereby influencing growth of tumour, invasion, and metastasis. [51]

Cellular Components

The TME includes a diverse range of cellular components, including:

1. Tumor cells: These are the cancer cells themselves, which are the primary focus of cancer research and treatment

2. Stromal cells: These are non-cancerous cells that offer structural and functional assistance to the tumor, comprising endothelial cells, fibroblasts, as well as immune cells such as lymphocytes and macrophages.

3. Immune cells: These cells, like B cells, T cells, and natural killer cells, are part of the body's defence against cancer, but can also play a role in advancing the development of the disease by fostering inflammation and angiogenesis.

4. Endothelial cells: These cells form the lining of blood vessels and play a vital role in angiogenesis, which is the process of developing new blood vessels to provide the tumor with nutrients and oxygen. [51,52,53]

Non-Cellular Components

The tumor microenvironment also comprises non-cellular elements that are crucial for its function:

1. Extracellular matrix (ECM): This constitutes a network of proteins and other molecules that offer structural reinforcement and govern cell behaviour.

2. Cytokines and growth factors: These are signalling molecules that are secreted by cells and can stimulate or inhibit cell growth, differentiation, and survival.

3. Chemokines: These are signalling molecules that attract immune cells to tumor locale, influencing the immune response. [53,54]

Functions of the Tumor Microenvironment

The TME performs several key functions that aid in the growth and advancement of cancer:

1. Angiogenesis: The TME fosters the creation of new blood vessels, providing the tumor with oxygen and nutrients.

2. Immune suppression: The TME can suppress the immune response, permitting the cancer cells to elude detection and destruction.

3. Inflammation: The TME can stimulate chronic inflammation, which can promote the growth and progression of the tumor.

4. Metastasis: The TME can facilitate the dissemination of neoplastic cells to other regions of the body by providing a permissive environment for their growth and survival.[54]

Therapeutic Implications

Grasping the structure and role of the TME is critical for formulating successful cancer therapeutic approaches. Directing interventions toward the TME holds potential as a viable strategy to combat cancer, as it can:

1. Disrupt angiogenesis: Preventing the formation of new blood vessels can deprive the tumor of vital nutrients and oxygen, thereby impeding its growth.

2. Enhance immune response: Stimulating the immune response can help the body recognize and eliminate cancer cells.

3. Inhibit inflammation: Reducing chronic inflammation can prevent the growth and progression of the tumor.

4. Prevent metastasis: Directing interventions toward the TME has the potential to inhibit the spread of oncogenic cells to distant locations in the body.

The tumor microenvironment stands as a multifaceted and ever-changing structure crucial in cancer's evolution, advancement, and therapeutic strategies. Comprehending its composition and function is essential for crafting effective cancer therapies that target the TME to combat the disease. [54, 55, 56]

Cancer Immunotherapy

Different immunotherapy approaches in cancer treatment encompass a variety of strategies geared towards maximizing the capability of immune system to effectively fight against cancer cells. Cancer immunotherapy approaches includes; Cancer vaccines, Checkpoint inhibitors and Adoptive cell transfer.

Checkpoint inhibitors:

Checkpoint inhibitors represent a type of immunotherapy designed to target checkpoint proteins, thus amplifying the immune system's capacity to identify and fight cancer cells more efficiently. These inhibitors, known as immune checkpoint inhibitors (CPIs), function by obstructing cell surface receptors of T lymphocytes, thus amplifying the antitumor immune response. [57] This class of immunotherapy stands as one of the most extensively researched to date and holds significant importance in treating various malignancies. Over the past decade, two particularly promising checkpoint inhibition approaches have garnered widespread use: blocking CTLA-4 and PD-1/PD-L1 molecules. [57,58] Other potential targets, including inhibitory receptors such as V-domain Ig suppressor of T-cell activation (VISTA), T-cell immunoglobulin and mucin 3 (Tim-3), and lymphocyte activation gene 3 (Lag-3), as well as activating molecules like glucocorticoid-induced TNFR-related protein (GITR) and OX40 (CD134), are presently being studied. [57-62]

Mechanism: Checkpoint inhibitors function by obstructing proteins on either immune cells or cancer cells called checkpoint proteins. Through this inhibition, checkpoint inhibitors aid in preventing the suppression of the immune system, thereby empowering it to effectively target and eradicate cancerous cells. [63]

Clinical Applications: Checkpoint inhibitors have been successfully used in managing various cancers like melanoma skin cancer, lung cancer, renal cell cancer, non-small cell lung cancer, kidney cancers, Hodgkin lymphoma, neck and head cancers, liver cancers, breast cancers, and urinary tract cancers. These inhibitors have demonstrated notable effectiveness in improving outcomes for patients with these malignancies. [63]

Recent Progress: Recent literature highlights the significant advancements in understanding how checkpoint inhibition by CTLA-4 blockade can alter the tumor-reactive T cell repertoire. This progress has led to unprecedented successes in immuno-oncology, marking a transformative revolution in cancer therapy. The latest insights and innovations in checkpoint inhibitors have contributed to remarkable achievements in clinical settings across various tumor types. [64]

Cancer vaccines:

Cancer vaccination, alternatively termed cancer immunotherapy or cancer immunization, encompasses a treatment strategy designed to trigger the immune system to identify and eliminate tumour cells. Its major aim is to hinder tumor progression, prevent reappearance, or metastasis, all while bolstering the immune system's capacity to detect and exterminate cancerous cells. Cancer vaccines work by stimulating an immune reaction targeted at specific tumor-associated antigens (TAAs), which are proteins produced by cancer cells. This immune response triggers the activation of B cells, T cells, and other immune cells, ultimately resulting in the elimination of cancer cells. Cancer vaccines function as preventative measures for high-risk groups, termed prophylactic vaccines, and as treatment options for those already diagnosed with

cancer, known as therapeutic vaccines. By harnessing the immune system's capabilities, cancer vaccination presents hopeful paths for both preventing and treating cancer. [65]

Moreover, adjuvants represent critical constituents of oncologic vaccinations, as they fortify immunological responses by triggering Instinctive immune pathways. Adjuvants, including Toll-like receptor (TLR) agonists, immune checkpoint inhibitors, and cytokines, are utilized to enhance the vaccine effectiveness. CpG oligodeoxynucleotides (CpG-ODNs) is a TLR agonists, which trigger antigen-presenting cells (APCs) to facilitate antigen presentation, whereas immune checkpoint inhibitors block inhibitory signalling pathways, thereby extending immune activation. These have yielded favourable findings in both preclinical research and clinical research., playing a role in the advancement of novel oncologic vaccines. Despite hurdles in the development of cancer vaccines concerning efficacy, multiple immunotherapeutic vaccination approaches are advancing through development and evaluation in preclinical trials and clinical trials. [66]

Mechanism of Action: Cancer vaccines work by introducing specific antigens or genetic material from oncogenic cells to the immune system, prompting it to identify these cancer-specific targets as non-self and provoke an immunological response against them. This immune response can cause the elimination of cancer cells and the formation of immunological memory to prevent cancer from recurring. [67]

Recent Advances: Recent literature highlights significant advancements in cancer vaccines, particularly in the progression of mRNA-based cancer vaccines. The success of mRNA-based COVID-19 vaccines has raised hopes for the application of mRNA therapeutics in cancer treatment. Studies have shown promising results from preclinical studies and clinical trials, identifying challenges such as an immunosuppressive tumor microenvironment, tumor heterogeneity, the most effective routes for vaccine administration, and the necessity for biomarkers for monitoring the treatment response. [68]

Adoptive cell transfer (ACT) is a cutting-edge form of immunotherapy that empowers the body's natural defenses to combat disease, particularly cancers that have proven resistant to traditional therapies. This technique revolves around manipulating a patient's immune system to create a personalized army of powerful cancer fighters. [69,70]

The core principle of ACT lies in isolating T cells, a vital component of the immune system responsible for immune responses. These T cells can come from two sources:

The patient themselves (autologous): T cells are extracted from the patient's blood and potentially even tumor tissue. These patient-derived cells are then amplified and activated in a lab setting before being reintroduced to the patient.

A healthy donor (allogenic): Donor T cells offer an alternative when a patient's own T cells are insufficient or dysfunctional. However, these cells require careful matching and manipulation to prevent rejection by the recipient's immune system [70,71,72]

Once obtained, T cells undergo a process of enhancement. This can involve:

Expansion: Techniques are used to significantly increase the number of T cells, creating a potent army.

Activation: T cells are stimulated to recognize and attack specific markers present on cancer cells. This can be accomplished through a variety of techniques; including exposure to tumor-specific antigens or genetic modification with chimeric antigen receptors (CARs) [71,72]

The reinfused T cells then become highly targeted warriors within patient's body. They actively seek out and destroy cancer cells, offering a personalized approach to cancer treatment.

While ACT holds immense promise, research continues to refine its effectiveness and address potential drawbacks. Challenges include the high cost of treatment, the possibility of severe side effects, and require for further optimization to ensure long-term efficacy against a diverse range of cancers. [73]

There are two main approaches within ACT:

Tumor-infiltrating lymphocyte (TIL) therapy: This method extracts T cells that have naturally infiltrated the patient's tumor. These T cells are subsequently activated and expanded in the laboratory and then reintroduced to the patient.

Chimeric antigen receptor (CAR) T-cell therapy: Here, T cells undergo genetic modification to express a specially designed receptor called a CAR. This CAR helps the T cells identify and target specific proteins on the exterior of cancer cells. [71,72,73]

CONCLUSION

The intricate challenges inherent in cancer immunotherapy demand a nuanced understanding and innovative approaches for effective treatment. Tumor heterogeneity, with its diverse immunological profiles, complicates therapeutic strategies, while tumors' sophisticated evasion mechanisms thwart immunotherapeutic interventions. Despite its transformative potential, immunotherapy encounters resistance mechanisms necessitating novel strategies for overcoming treatment limitations. Biomarker identification remains elusive, hindering personalized treatment approaches tailored to individual patients. Moreover, immunomodulatory side effects, such as autoimmune reactions, underscore the need for rigorous management strategies to optimize treatment safety and efficacy. Addressing these challenges is paramount for advancing cancer immunotherapy and improving patient outcomes. Precision immunotherapy utilizes genomics and

immunogenomics to tailor treatment to individual immune profiles. Combination therapies merge immunotherapies with targeted agents and conventional treatments to overcome resistance and enhance efficacy. Development of novel immunomodulatory agents targets immune checkpoints, tumor microenvironment components, and metabolic pathways to boost immune responses. Biomarker discovery integrates multi-omics approaches and advanced imaging for personalized treatment. Investigation of synergies between immunotherapy and modalities like radiotherapy, chemotherapy, and oncolytic viruses enhances treatment outcomes. These strategies promise to revolutionize cancer care by optimizing treatment effectiveness and minimizing adverse effects.

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