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Review Article

Cancer Immunotherapy: Bridging Concept with Practice – A Broad-Brush Stroke

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Abstract

Cancer presents a significant global health challenge, expected to worsen due to factors like population growth and aging, standing as a leading cause of death worldwide with nearly 10 million lives lost in 2020 alone. Understanding the immune system's impact on cancer growth is crucial for developing effective Cancer Vaccines (CVs) and other immunotherapies, despite posing complex challenges in immunology. Immunotherapy has emerged as a groundbreaking strategy, using the body's immune system to target and eliminate cancer cells, with approaches such as immune checkpoint inhibitors, CAR (Chimeric Antigen Receptor) T-cell therapy, CVs, and oncolytic viruses offering unique advantages. However, challenges persist, including immune suppression by cancer cells, immune system recognition issues, and weakened immune systems in cancer patients. Combination immunotherapy aims to enhance cancer cell recognition and kill by addressing various immune evasion mechanisms. Advancements in sequencing technologies enable personalized immunotherapies by analyzing individual tumor genetic makeup to target specific mutations or molecular pathways, enhancing treatment effectiveness. Another critical area of research involves the Tumor Microenvironment (TME) and its impact on immune responses, with strategies to modulate the TME potentially enhancing the effectiveness of CVs and other immunotherapies. Despite challenges, immunotherapy, including CVs, remains promising, with ongoing research offering potential for transformative treatments and improved patient outcomes, underscoring the importance of continued investment in research and novel immunotherapeutic strategies. In particular, as we deepen our comprehension of the immune system's complex mechanisms and its interactions with cancer cells, we can discover new avenues for more efficient and personalized treatments.

Keywords: Cancer; Immunotherapy; Cancer vaccines; Tumor microenvironment; Leukemia

Introduction

Global cancer burden and trends

Cancer presents a pressing global health challenge that worsens due to population growth and aging [1]. In 2018, there were an estimated 17 million new cases and 9.5 million deaths globally, with projections indicating an increase to 27.5 million new cases and 16.3 million deaths by 2040. Cancer accounts for a significant portion of Disability-Adjusted Life Years (DALYs) and cancer-related fatalities, representing 42% and 44% respectively. Between 2010 and 2019, there was a 16.8% increase in DALYs and a 20.4% increase in cancer deaths globally, with metabolic risks also on the rise [2,3]. Factors such as smoking, poor diet, physical inactivity, and reduced childbirth in developing countries is expected to contribute to the growing burden [4]. Cancer is a leading cause of death worldwide, responsible for nearly 10 million deaths in 2020, or about one in six deaths [2]. Interestingly, cancer incidence is higher in men, with a 19% higher incidence rate for all cancers combined compared to women [5].

The Complexity of Cancer: Understanding its Nature and Origins

Cancer presents a multifaceted group of diseases, encompassing over a hundred distinct types, each displaying unique behavior and responses to treatment. It arises from uncontrolled cell proliferation, leading to tumor formation. Distinguishing between benign and malignant tumors is critical in cancer pathology; benign tumors, like common skin warts, remain localized and do not invade surrounding tissues or spread to distant sites, while malignant tumors can metastasize through the circulatory or lymphatic systems, posing a significant threat as they infiltrate and spread throughout the body [6,7].

The quest to unravel the mysteries of cancer spans centuries, with ancient observations shaping our current understanding. Early accounts by Hippocrates coined the term "cancer," describing tumors with crab-like extensions [8]. Later scientific revelations, including those by Hooke and Virchow, unveiled the cellular composition of tissues, prompting investigations into the origins and behavior of cancer cells [6]. Cancer development is shaped by two key groups of genes: proto-oncogenes, which, upon mutation, transform into oncogenes and stimulate excessive cell division, and tumor suppressor genes, which, when mutated and inactive, fail to regulate cell division, leading to uncontrolled growth [9].

Cellular senescence, a state of non-proliferation, serves as a protective mechanism against cancer. However, cancer cells can evade senescence, contributing to cancer initiation, progression, and response to treatment [10]. Solid tumors demand substantial oxygen and nutrients, prompting the development of their vascular supply through angiogenesis. Nonetheless, this vascular supply often falls short, creating a hostile TME (Tumor Microenvironment) characterized by hypoxia, nutrient deficiency, acidity, and elevated interstitial fluid pressure [11,12]. Taken together, cancer is a complex disease influenced by various factors, including genetic mutations,

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cellular processes, and the TME. Understanding these complexities is paramount in devising effective treatments and strategies to combat this disease.

Underlying Immune Mechanisms of Cancer Pathophysiology

Understanding the impact of the immune system on cancer growth and spread has been a challenging issue in immunology [13,14]. The development of a CV and other immunotherapies relies on understanding how the immune system influences the onset and spread of cancer [15,16]. Over the past three decades, research has explained the complexity of our immune system, revealing why a comprehensive cure for cancer has been difficult to achieve. This accumulated knowledge has shown the dual nature of the immune system, which can both inhibit tumor growth by eliminating cancer cells through immune attack or preventing their outgrowth, and accelerate cancer progression by favoring tumor cells that can survive in an immunocompetent host or by creating conditions in the TME that support tumor growth [14,17]. Using an analogy, we can liken the immune system to a conductor leading the body's defense against cancer. However, there are times when its actions unintentionally aid tumor growth, similar to how a misplaced musical note disrupts harmony. This understanding has led to the conceptual framework of "cancer immunoediting", which integrates the immune system's dual tumor-protective and tumor-promoting activities [18,19]. The term was coined following a seminal 2001 study in mice, demonstrating that tumors in mice with compromised immune systems were generally more immunogenic ("unedited") than those in mice with intact immune systems ("edited") [20]. This concept has sparked extensive research, forming the basis of the highly debated cancer immunoediting theory.

The three progressive distinct phases encompass cancer immunoediting

The TME, where cancer immunoediting takes place, can be delineated into three discrete stages: elimination, equilibrium, and escape [21,22]. The process commences with elimination, during which the innate and adaptive immune systems collaborate to eradicate the emerging tumor, leading to tissue normalization and tumor cell destruction. However, if the immune response falls short of completely eliminating the tumor, the tumor may enter an equilibrium phase, wherein its growth is constrained by immune surveillance, yet the tumor persists. Conversely, the escape phase of cancer immunoediting marks the clinical emergence of the disease, as the tumor evades immune attack and spreads to distant organs. This phase may result from continued immune pressure on the tumor, fostering a microenvironment conducive to tumor survival and growth. The tables (Table 1 and 2) describe the immune cells and released factors, such as cytokines, involved in the entire process of immunoediting within the TME.

Therapeutic Interventions of Cancer: Different Approaches to Immunotherapy

Immunotherapy has emerged as a revolutionary strategy in cancer treatment, utilizing the body's immune system to identify and eliminate cancer cells [15-17,86]. Unlike traditional treatments that directly target tumors, immunotherapy enhances the immune response against cancer. This field encompasses a wide range of techniques and approaches, each with its own unique mechanisms and potential benefits.

Hence, this section explores the diverse array of immunotherapy methods for cancer, showcasing the variety of strategies employed by researchers and healthcare providers. These approaches include Immune Checkpoint Inhibitors (ICTs), CAR T-cell therapy, CVs, and Oncolytic Viruses (OVs), each offering distinct advantages and challenges in harnessing the immune system to combat cancer effectively (Figure 1) [87]. By examining these different methods, we gain a deeper understanding of the options available for personalized cancer treatment and pave the way for innovative therapeutic interventions.

Immunomodulation

Immunomodulation aims to enhance the body's immune response by activating the immune system [88]. One approach involves stimulating Antigen-Presenting Cells (APCs) to present tumor antigens to Cytotoxic T Lymphocytes (CTLs), leading to increased tumor cell destruction [89]. Cytokines are key immunomodulation agents, and several cytokine-based immunomodulators are approved for different cancer types [90]. For example, Aldesleukin (Proleukin®), a synthetic version of IL-2, is used to treat melanoma and kidney cancer [91].

Another group of immunomodulators used in cancer immunotherapy are checkpoint inhibitors, which block proteins that prevent the immune system from attacking cancer cells [92]. These inhibitors target proteins on T cells or cancer cells involved in immune system regulation. By inhibiting these mechanisms, the body's natural anti-tumor response can be supported and enhanced. For instance, ipilimumab (Yervoy®) is used to treat advanced melanoma by blocking CTLA-4 (Cytotoxic T-Lymphocyte Associated Protein 4), a protein that suppresses immune responses. Blocking CTLA-4 boosts T cell attack on tumor cells without affecting healthy cells [93].

Immunomodulatory Monoclonal Antibodies (mAbs), such as nivolumab, which blocks the programmed Cell-Death Protein-1 (PD-1) receptor, have shown anti-tumor activity and are FDA (Food and Drug Administration)-approved for melanoma and Non-Small-Cell Lung Cancer (NSCLC). These treatments target immune cells rather than cancer cells, making them potentially effective across different cancer types [92,94].

Adoptive cell therapy

Adoptive Cell Therapy (ACT) is a type of immunotherapy where patients receive T cells, a crucial component of the immune system, to aid in fighting diseases like cancer [95,96]. These T cells are typically harvested from the patient's blood or tumor tissue, expanded in a laboratory setting, and then reintroduced into the patient's body to bolster the immune response against the disease. In certain instances, these T cells undergo genetic modification in the lab to enhance their ability to target and eliminate cancer cells. ACT encompasses approaches such as CAR-T cell therapy, Tumor-Infiltrating Lymphocyte (TIL) therapy, and T Cell Receptor (TCR) therapy [95,96].

TIL therapy involves harvesting T cells that have already infiltrated the patient's tumor tissues, expanding them in culture, and reintroducing them to the patient to enhance their cancer-fighting capabilities. However, a challenge of TIL therapy is generating a sufficient number of cells *in vitro* for effective treatment. TCR therapy allows for the genetic modification of T cells from peripheral lymphocytes, activating and expanding anti-tumor T cells to target

Table 1: Immune Components of the Tumor Microenvironment (TME) Participate in the Entire Immunoediting Process.

Cell Type	Description	Role in the TME
TA	Cells bearing tumor antigen [23].	Antigenic function
NKR Ligands	Natural Killer (NK) cell receptors recognize ligands on target cells, including MHC class I molecules for inhibition and stress-induced molecules like MICA/MICB (MHC class I chain related-proteins A (MICA) and B (MICB) for activation. Viral proteins and tumor-associated antigens can also trigger NK cell responses. The balance of activating and inhibitory signals determines NK cell activity against infected or abnormal cells [24,25].	They block the activation of Natural Killer (NK) cells. Decreasing the levels of Natural Killer Receptor (NKR) ligands results in the activation of NK cells in the Tumor Microenvironment (TME), enhancing their ability to kill tumors [25].
Mφ	Macrophages	An element of the innate immune system, Tumor-Associated Macrophages (TAMs), predominantly of the M2 type in many instances, typically hinder the recruitment and activity of T cells, thereby reducing the anti-tumor impact of cytotoxic T cells. In contrast, M1 TAMs eliminate cancer cells by stimulating adaptive immunity through proficient antigen presentation and the induction of anti-tumor IFN-gamma production [26,27].
TAN	Tumor-Associated Neutrophils (TANs).	The two types of Tumor-Associated Neutrophils (TANs), N1 and N2, exhibit contrasting effects on cancer progression. N1 neutrophils possess anti-tumor properties, while N2 neutrophils display pro-tumor characteristics [28,29].
NK	Natural killer cells.	One subset of the innate immune system demonstrates anti-cancer traits in the early stages of cancer development before becoming senescent as the disease advances [30,31].
NKT	Natural killer T cells.	Another subset of the innate immune system initially functions as anti-tumor agents before becoming exhausted as the cancer progresses [32].
MDSC	Myeloid-derived suppressors.	They comprise a diverse group of immature myeloid cells recruited to the TME to create an immunosuppressive environment that supports cancer growth [33].
CD4+T	Helper T cells	The adaptive immune response against cancer is driven by CD4+ T helper cells, mainly through the activation of cytotoxic CD8+ T cells [34].
CD8+T	Killer T cells	In the TME, CD8+ T cells play a crucial role in tumor immunity. Upon entering the TME, CD8+ T cells mature into cytotoxic T cells, which are capable of killing tumor cells [35].
Treg	Regulatory T cells	They hinder the activation and differentiation of CD4+ and CD8+ T cells. Regulatory T cells (Tregs) present in the TME obstruct anti-tumor immunity and bolster cancer progression [36].
B	B lymphocytes	In addition to T cells, the TME also includes a second group of adaptive immune cells known as B cells. B cells can combat tumors by generating antibodies against Tumor-Specific Antigens (TSAs), serving as Antigen-Presenting Cells (APCs), or directly targeting cancer cells for destruction [37]. However, they can also promote tumor growth by activating MDSCs, producing pro-tumorigenic cytokines, and stimulating immunosuppressive Tregs [38,39].
Breg	Regulatory B cells	B regulatory cells (Bregs) proliferate within tumors and can generate immunosuppressive cytokines like IL-35 and IL-10, dampening anti-tumor immune reactions [40]. Furthermore, IL-35 produced by B cells can suppress the responses of effector CD4+ and CD8+ T cells while promoting the proliferation of Tregs, thereby exacerbating cancer progression by reducing the anti-tumor immune response [41].
DCs	Dendritic cells	Dendritic Cells (DCs) play a crucial role in presenting antigens to both T cells and B cells. Typically, DCs are key players in initiating and sustaining anti-tumor immune responses [42]. However, in the TME, their ability to present antigens may be compromised or diminished. Additionally, DCs in the TME can transform into regulatory DCs with immunosuppressive properties. These regulatory DCs can restrict the anti-tumor function of effector CD4+ and CD8+ cells in the TME, thereby promoting tumor growth and progression [43,44].
γδT	Gamma delta T cells	Gamma-delta (γδ) T cells are a unique subset of atypical T cells situated at the interface between innate and adaptive immunity [45]. They possess the remarkable ability to recognize tumor antigens without the need for Major Histocompatibility Complex (MHC) restriction, a characteristic more commonly associated with innate immune cells [46]. In the TME, γδ T cells can exhibit both pro-tumor and anti-tumor functions [47]. On one hand, they may prevent T-cell cytotoxicity and DC maturation, and promote the expansion of immunosuppressive tumor-infiltrating neutrophils. On the other hand, when activated, γδ T cells can enhance the anti-tumor activities of adaptive immune cells [48].

Table 2: Cytokines in Tumor Microenvironment (TME) Linked to Cancer Immunoediting.

Type	Origin	Function in the TME
IL-6	Interleukin-6 (IL-6) is produced by macrophages that are associated with tumors (TAMs) [49].	Pro-tumor characteristics encompass a range of behaviors, including the expansion of Neutrophils (Ns) and the antagonism of the Treg population [50]. These actions lead to the proliferation of tumor cells, increased angiogenesis, enhanced tumor survival, and metastasis [51]. Conversely, examples of anti-tumor capabilities include increased T cell survival and proliferation to bolster adaptive immunity, as well as enhanced trafficking of CD8+ T cells to the TME and lymph nodes [52].
IL-10	Both cancer cells and various immune cells, including those from the myeloid and lymphoid lineages, secrete IL-10 [53].	Pro-tumor activities encompass actions such as promoting increased survival and proliferation of tumor cells, as well as inducing metastasis [54]. These effects are primarily mediated by the immunosuppressive actions of IL-10 on other effector immune cells that would otherwise restrict cancer progression, such as potent anti-tumor cytotoxic NK cells and CD8+ T cells [55].
IL-12	Produced by dendritic cells (DCs), macrophages (Mφs), Neutrophils (Ns), and B cells [56].	IL-12 triggers an effector immune response against tumor cells by promoting the polarization of M1 macrophages and the production of IFN-γ by Th1 cells. These actions, in turn, enhance the activity of anti-tumor cytotoxic CD8+ and NK cells, ultimately leading to an effective anti-tumor response [57,58].
IFN-γ	Produced by Natural Killer (NK) cells and T cells, including CD4+ T helper cells [59].	IFN-γ enhances the expression of MHC class I molecules on tumor cells, thereby increasing the antigenicity of tumor-associated antigens. This leads to more efficient antigen presentation, especially for recognition by anti-tumor adaptive immune cells within the TME [60,61]. For instance, IFN-γ boosts the cytotoxic capabilities of NK cells and CTLs (Cytotoxic T-Lymphocytes) [62].
IFN-α/β	Produced mainly by fibroblast cells, IL-6 is also produced by cancer cells and Dendritic Cells (DCs) [63].	IFN-α/β is classified as a type I interferon, whereas IFN-γ is categorized as a type II interferon. Its anti-tumor properties include the activation of CTLs, T-helper cells, NK cells, and macrophages (Mφs) [64]. Additionally, it inhibits angiogenesis and promotes apoptosis in cancer cells [65].
TNF-α	While macrophages (Mφs) and Neutrophils (Ns) are the main sources of the pro-inflammatory cytokine TNF-α among innate immune cells, T and B lymphocytes, NK cells, as well as non-immune cells like endothelial cells, mast cells, and fibroblasts, can also produce TNF-α under certain conditions [66,67].	TNF-α has been recognized as a pivotal factor in orchestrating inflammation in both benign and malignant tumors, capable of inducing rapid hemorrhagic necrosis of tumors [68].
TGF-β	TGF-β (transforming growth factor-beta) is secreted by various cell types, including macrophages (Mφs), cancer cells, and others [69].	The release of TGF-β within tumors creates a TME that supports tumor development, invasion, and metastasis through autocrine and paracrine mechanisms. Additionally, TGF-β exerts immunosuppressive effects on all components of the immune system, significantly impairing its ability to recognize and eliminate cancer cells [70,71].
NKG2D	NKG2D is a transmembrane protein receptor that is produced and displayed by Natural Killer (NK) cells, gamma-delta (γδ) T cells, and CD8+ T cells [72]. Despite its initial discovery on NK cells, NKG2D is highly conserved and expressed on various innate and adaptive lymphocytes, including invariant Natural Killer T (iNKT) cells and innate lymphoid cells [73].	NKG2D enhances the anti-tumor response in the TME by upregulating its expression in NK and CD8+ T cells, thereby restricting the progression of cancer [74].
TRAIL	TNF-Related Apoptosis-Inducing Ligand (TRAIL) is found in various types of host cells [75].	TRAIL can induce apoptosis in cancer cells by binding to both its membrane-bound receptors and a soluble receptor [76].
Perforin	A cytolytic protein predominantly found in CD4+ T cells and natural killer (NK) cells [77].	Perforin and granzymes-mediated cytotoxicity are the most effective method of eliminating tumor cells [78].
Galectin-1	Gal-1, one of the beta-galactoside-binding proteins, is expressed to varying degrees on immunological and endothelial cells. However, it is often found in significant amounts and produced abundantly by cancer cells [79].	Tumor-secreted Gal-1 contributes to immune evasion by binding to immune cells and suppressing their anti-tumor functions within the TME [80].
IDO	Dendritic Cells (DCs) associated with tumors and endothelial cells express indoleamine 2,3-dioxygenase (IDO) [81].	IDO promotes cancer immunotolerance by suppressing the immune system, limiting T cell proliferation and activation, which allows it to exhibit its pro-tumor characteristics [82].
CTLA-4	CTLA-4 (cytotoxic T-lymphocyte–associated antigen 4) is expressed by activated CD4+T cells and regulatory T (Treg) cells [83].	CTLA-4 plays a role in controlling the body's immunological responses. When CTLA-4 binds to the protein B7, it prevents T cells from killing other cells, including cancer cells.
PD-1	Programmed cell death protein-1 (PD-1).	PD-1 is a receptor that specifically binds to PD-L1 [84]. Once bound, PD-1 can inhibit lymphocyte activation, reduce lymphocyte cytokine release, and ultimately increase lymphocyte apoptosis, leading to immunotolerance that promotes tumor growth [85].

specific cancer antigens while sparing normal cells. In CAR-T cell therapy, a patient's T cells are modified outside the body with a CAR designed to target a specific tumor antigen. This approach enables the recognition of cancer cells independent of Major Histocompatibility Complex (MHC) presentation and can be customized to target different cancer types. FDA and EMA (European Medicines Agency)-approved CAR-T therapies like Kymriah® and Yescarta® for lymphoma treatment underscore the potential of ACT in cancer therapy [97].

Antibodies

Antibodies play a crucial role in targeting various factors within the TME that suppress anti-tumor immune responses, promote tumor cell development, and stimulate pro-tumorigenic angiogenesis. Targeting these mechanisms has shown clinical efficacy in combating

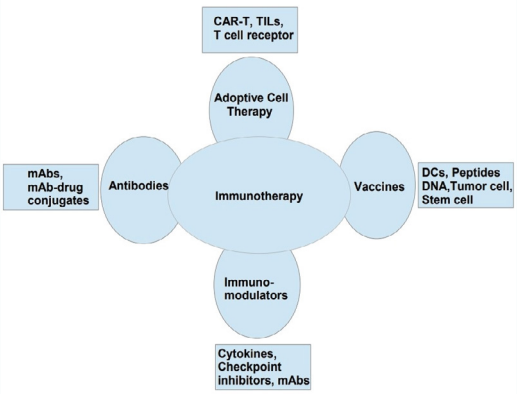

Figure 1: Recent approaches to cancer immunotherapy. Dendritic Cells (DCs); Chimeric Antigen Receptor T cells (CAR-T); Tumor Infiltrating Lymphocytes (TILs).

tumor growth. Specifically, mAbs can induce tumor cell death through several mechanisms, particularly by targeting antigens specific to or overexpressed by tumor cells [98,99].

One of the primary mechanisms by which antibodies induce tumor cell death is by inhibiting growth factor receptor signaling. By binding to growth factor receptors, mAbs can alter their activation state or prevent ligand binding, disrupting pro-tumor growth and survival signaling. For example, cetuximab, an anti-EGFR (Epidermal Growth Factor Receptor) mAb, induces apoptosis in tumor cells by blocking ligand binding and receptor dimerization [100].

Additionally, antibodies can exert their effects through indirect mechanisms that involve the host immune system. These mechanisms include Complement-Dependent Cytotoxicity (CDC), Antibody-Dependent Cellular Phagocytosis (ADCP), and Antibody-Dependent Cellular Cytotoxicity (ADCC) [101,102]. In ADCP, macrophages expressing FcγRI bind to IgG1 or IgG3 mAbs that have opsonized tumor cells, leading to phagocytosis. ADCC, on the other hand, involves antibodies binding to antigens on target cells and linking them to effector cells, which then kill the target cells.

Furthermore, Antibody Drug Conjugates (ADCs) are designed to deliver a cytotoxic drug specifically to cancer cells while sparing normal tissue [103,104]. ADCs consist of an antibody specific to the cancer cell, a cytotoxic drug, and a linker protein. This targeted approach, often referred to as a "smart bomb" against cancer cells, has shown promise in treating various cancers. Several ADCs have been approved for the treatment of blood cancers and breast cancer, with many more in clinical trials. Ado-trastuzumab emtansine (Kadcyla; Genentech), for example, targets the ERBB2 (v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2) protein on the surface of some breast cancer cells, demonstrating the potential of ADCs in cancer therapy [105].

Cancer vaccines

CVs aim to activate the immune response against specific cancer cell antigens, stimulating antibody production and CTLs to target cancer cells [15,16,106,107]. Recent advancements in ICTs and CAR-T cell therapies underscore the immune system's role in fighting cancer, particularly through T cells [83-85]. Challenges persist, especially in diseases like cancer and HIV (Human Immunodeficiency Virus) where robust cellular responses are crucial [108,109]. While CVs have shown success in generating antibody responses, improving cellular responses remains a priority [110]. Thus, a comprehensive assessment of current strategies and advancements is needed to enhance existing vaccines and develop new approaches for better cancer treatment.

Mechanisms of resistance to cancer immunotherapies

A variety of mechanisms play crucial roles in resisting cancer immunotherapies, including CVs. For instance, CD8+ T cells express immune checkpoint molecules that can limit their functions, potentially allowing tumor cells to deplete vaccine-induced CD8+ T cells and promote cancer progression. Notably, CTLA-4 (Cytotoxic T-Lymphocyte Associated Protein 4) and PD-1 (Programmed Cell Death Protein 1) are the most targeted pathways involved in immune escape by tumors (Figure 2) [83-85].

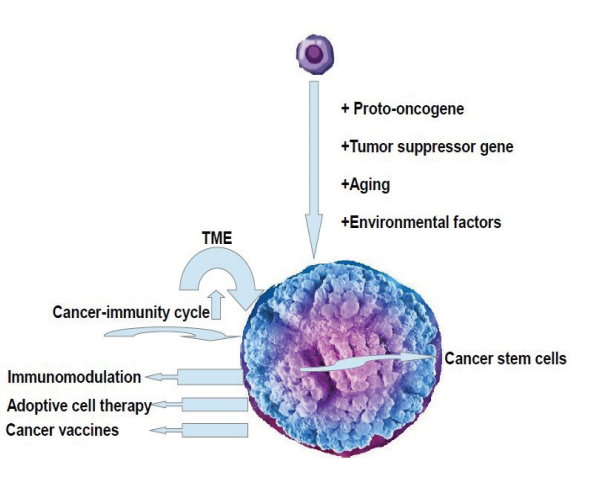

Figure 2: A simplified graphical representation of the cancer immunotherapy. Cancer cells form as a result of mutations in tumor suppressor genes and proto-oncogenes. Besides, aging and environmental factors including psycho-socioeconomic factors also have an impact on the prevalence of cancer. Cancer-immunity cycle activation leads to an immunosuppressive milieu inside the Tumor Micro Environment (TME), which promotes the growth of malignant tumor cells. The cancer stem cells are hidden within the tumor bed, and are frequently challenging to eradicate using current immunotherapeutics. The progression of cancer disease can be halted by immunotherapies such as immunomodulation (cytokines and Immune Checkpoint Inhibitors (ICIs)), adoptive cell therapy (CAR-T, NK cells etc.), and Cancer Vaccines, etc. (CVs), either alone or in combination. To produce the final image, several individual components from Google Images were customized before being assembled.

Additionally, regulatory T cells (Tregs) characterized by CD (Clusters of Differentiation) 4+CD25+FoxP3 (Forkhead Box Protein 3)+T cells perform immunosuppressive activities in the TME, driving tumor progression [36,111]. Tregs secrete pro-inflammatory cytokines such as TNF (Tumor Necrosis Factor)-α, IL (Interleukin)-1β, and IL-12 in a Signal Transducer and Activator of Transcription 3 (STAT-3)-dependent pathway, contributing to immune evasion by the tumor. Moreover, Tregs secrete IL-35, which inhibits CD4+T cells and CD8+ T effector proliferation *via* IL-35-mediated activation of STAT4 and STAT1 [112].

Aberrant Wnt (Wingless-related integration site)/β-catenin signaling can also promote tumor growth, invasiveness, and metastatic potential, while preventing Dendritic Cells (DCs) from migrating into the TME [113]. This reduces the presentation of tumor antigens to T cells, inhibiting the activation and cytotoxic effects of T effectors. Furthermore, IL-10 and IL-35 enhance CD8+ T cells' production of

inhibitory molecules, increasing their vulnerability to exhaustion and suppression [114]. Immunological checkpoint molecules such as CTLA-4 and *LAG3* (Lymphocyte Activation Gene 3) are expressed on Tregs' surface to target DCs and block their Antigen-Presenting Cell (APC) activity [115].

The gut microbiome is an important host factor that may regulate responsiveness and resistance to cancer immunotherapies [116,117]. Interaction between the gut microbiome and TAAs (Tumor-Associated Antigens) likely increases antigen presentation and inflammatory cytokine production by DCs [118]. Recent research suggests a strong connection between immune checkpoint proteins and gut bacteria in terms of the anti-tumor response [119]. Moreover, obesity may cause dysfunctions in anti-tumor CD8+ T cells, contributing to the development of cancer [120].

Understanding cancer vaccines and overcoming tumor immune evasion

Exploring the intricacies of CVs is crucial, considering the challenges in their development due to tumor complexity. The goal is to identify effective antigens that can trigger immune responses, enhancing tumor visibility to the immune system. Numerous host factors both intrinsic and extrinsic, influence tumor immune evasion, particularly during its early stages. Targeting these factors before cancer fully develops is vital [121, 122].

Cancer cells can evade immune responses by downregulating antigen processing and MHC (Major Histocompatibility Complex) presentation machinery, as well as suppressing TAA expression, partly through immunoediting [18-22]. This hinders vaccine-induced anti-tumor T cells from penetrating tumors and overcoming the immunosuppressive TME. Low immunogenicity, established tumor burden, and the TME pose significant challenges for developing preventive and therapeutic cancer vaccines. A promising approach involves generating tumor-specific CD8+ T lymphocytes while remodeling the TME using CVs [123,124].

Advancing Cancer Vaccine Development

The development of CVs hinges on using Tumor-Specific Antigens (TSA) and TAA to activate the immune system, aiming to stimulate both cellular and antibody-mediated immunity to inhibit tumor growth [23,125,126]. Unlike traditional vaccines, TAA and TSA are weakly immunogenic, posing a challenge. While traditional vaccines mainly promote humoral immunity, CVs seek to enhance CD8+ CTL-mediated immunity against tumor cells [15,16,106,107,127]. Prophylactic CVs aim to reduce cancer incidence and improve prognosis by halting specific tumor growth [128]. Five FDA-approved vaccines target cancer-causing viruses, providing protection against HPV (Human Papillomavirus) and HBV (Hepatitis B Virus) [129]. Therapeutic vaccines, on the other hand, target existing tumors, enhancing pre-existing immunity [130]. However, their efficacy has been modest, mainly due to the use of non-mutated self-antigens. In contrast, mutated neo-antigens like TAA and TSA can trigger stronger immune responses by bypassing immunological tolerance against self-antigens [131]. Advances in proteomics and genomics allow for the identification of ideal tumor antigens carrying mutations or neo-antigens, leading to personalized CVs and offering new hope in cancer treatment [132].

Challenges in developing prophylactic cancer vaccines

Clinical advancements in imaging and diagnostics have improved early cancer detection, creating a window for preventive vaccines to induce anti-cancer immunity before disease onset [133]. However, there are currently no preventive non-viral CVs in use due to the lack of ideal TAA and the risk of autoimmunity from cross-reactivity with self-antigens [134]. The immune system's tolerance mechanisms and the complexity of selecting an antigen for CVs pose challenges. Despite these hurdles, inducing anti-TAA immune responses prophylactically could potentially reduce cancer incidence and associated healthcare costs [135].

Advancing therapeutic cancer vaccines

Therapeutic CVs stimulate the immune system with tumor antigens to trigger an anticancer response, though they have shown less success in advanced cancer compared to newer therapies like immune checkpoint blockade or CAR T-cell therapies [136,137]. However, they remain a viable approach in solid tumors' immunotherapy. Progress in therapeutic CVs, from autologous tumor cell vaccines to dendritic cell vaccines like Sipuleucel-T (Provenge) for prostate cancer, has been significant [138]. The COVID-19 pandemic has renewed interest in CVs, highlighting the need for more efficient technology platforms for vaccine and tumor antigen production. Challenges in therapeutic CVs include immune suppression by cancer cells, immune system recognition, and weakened immune systems in cancer patients. Current research aims to enhance the presentation and recognition of vaccine antigens, improve the recruitment and maturation of Antigen-Presenting Cells (APCs), activate CD8+ T-cells, and optimize the TME for immune response [123]. Multiple clinical trials are underway globally to explore the clinical utility of therapeutic CVs [139,140].

Enhancing tumor antigen selection for improved cancer vaccine development

The immunosuppressive TME and the limited specificity of current tumor antigens have hindered effective CV development [15,16,23,38,80,87,107,109]. Combining vaccines with other immunotherapies can address this, but identifying new TAA and TSA is crucial for inducing targeted anti-tumor responses. Early vaccines used broad antigen repertoires but faced challenges with immune tolerance and logistical issues. Recent vaccines focus on specific, highly immunogenic antigens to overcome these hurdles.

Developing cancer vaccines targeting tumor-associated antigens

In simpler terms, CVs that target TAAs displayed on MHC molecules have the potential to activate a strong, tumor-specific immune response by CTLs, which can lead to the destruction of tumor cells and regression of cancer [15,16,141]. Table 3 illustrates T cell recognition of specific TAAs that can be utilized in vaccine development.

TAAs typically include cancer/testis antigens found in immune-privileged germ cells, tissue differentiation antigens, and antigens that are overexpressed in cancer cells [142-144]. When TAAs reach a certain level, overexpressed and tissue differentiation antigens can trigger an immune response against cancer, bypassing the body's tolerance to self-antigens. However, there is still a risk of causing autoimmune reactions against normal tissues that express similar antigens, which is a potential limitation of using these antigens in vaccines [16,107,109]. Moreover, the immune system may eliminate T cells with low affinity for these antigens through peripheral and central tolerance mechanisms, reducing the effectiveness of CVs

Table 3: Examples of Tumor-Associated Antigens Recognized by T-cells.

Type of TAA	Antigen	Type of Tumor and Origin	Normal Tissue Distribution
Cancer-testis (CA) [142]	BAGE, GAGE, MAGE, NY-ESO-1 (New York esophageal squamous cell carcinoma 1), SSX (synovial sarcoma X chromosome break point).	Melanoma, lymphoma, lung, bladder, colon, and breast carcinoma.	Spermatocytes/ spermatogonia of testis, placenta, and ovary cells.
Cell differentiation [143,144]	Gp100 (glycoprotein 100), Melan A/Mart-1 (melanoma antigen recognized by T cells-1), Tyrosinase, PSA (prostate-specific antigen), CEA (carcinoembyonic antigen), Mammaglobin-A, NY-BR-1; breast differentiation antigen, MUC-1 (mucin-1).	Melanoma, prostate cancer, colon and breast carcinomas.	Melanocytes, epithelial tissues, prostate, colon
Overexpreesed proteins [144145]	WT-1 (Wilms' tumor-1), Her-2 (human epidermal growth factor receptor 2) /neu, CEA (carcinoembronic antigen), p53, livin, survivin, Ribosomal P0 protein, Ribosomal protein S6, Ribosomal protein L19, HSPs (heat shock proteins), OPN (osteopontin), MYC, MDM2 (murine double minute 2), Mesothelin	Esophagus, liver, pancreas, colon, breast, ovary, bladder, lung, pancreas and prostate carcinomas, AML, urinary tract, neuroblastoma, small cell lung cancer, retinoblastoma, mesothelium, ovary.	Ubiquitous

using TAAs [145].

Cancer-testis antigens have become promising targets for vaccine immunotherapy due to their specificity to tumors and strong ability to provoke an immune response without activating self-tolerance [142]. Clinical trials are ongoing to evaluate the effectiveness and safety of cancer vaccines based on TAAs in various cancer types [144,146]. Examples of such trials include NCT01479244 (phase 3 trial for breast cancer), NCT00094653 (phase 3 trial for metastatic melanoma), NCT00090493 (phase 2/3 trial for multiple myeloma), and NCT00020787 (phase 3 trial for esophageal/gastric cancer).

Developing cancer vaccines targeting tumor-specific antigens

The limited success of CVs using TAAs has led to the exploration of new approaches, including TSAs like mutated neoantigens, oncoviral antigens, and endogenous retroviral elements [147,148]. Mutated neoantigens, arising from genetic mutations, differentiate tumor cells from healthy cells and can be targeted by CD8+ T cells. The response to ICTs often correlates with a high tumor mutation burden, indicating a potent anti-tumor response induced by TSAs. Current clinical trials are using mutated neoantigens to target various cancer types [149,150]. Selecting the right tumor antigens is crucial for therapeutic CV development, offering a safe and long-lasting immunotherapy alternative. Challenges like TAAs' co-expression on normal cells and patient-specificity of TSAs need to be overcome, possibly through modified TAA peptides and further validation of unconventional antigens [149-151].

Development of Therapeutic Cancer Vaccines and Technology Platforms

Over the years, CV development has prioritized stimulating T-cell-mediated immune responses against cancer cells, given T cells' ability to target intracellular pathogens [152-154]. Antigens presented on APCs in lymphoid organs, leading to T-cell multiplication and differentiation into effector cells, trigger t-cell responses. These effector T cells must act quickly upon reaching the tumor site. In contrast, B cells, while important, produce antibodies with broader but less potent effects against cancer cells [155,156]. The focus on T-cell responses represents a shift from past reliance on B-cell activation, akin to prophylactic vaccines. Advances in understanding T cell activation have improved therapeutic CVs, which include cellular, virus vector, and molecular platforms (peptides, DNA, RNA), each with distinct advantages and challenges [145,146,157,158]. Therefore, the following section of this article explores the conceptual advancements and challenges associated with developing CVs, considering the evolving understanding of disease pathology and immune mechanisms.

The origin and development of cellular vaccines

Cell-based vaccines, such as tumor cell and immune cell vaccines have been studied for over a century. Paul Ehrlich first suggested using weakened tumor cells as a vaccine to target cancer, sparking global research into CVs using irradiated whole tumor cells [159]. These vaccines, whether derived from a patient's own tumor cells or from irradiated tumor cell lines, offer the advantage of presenting a variety of tumor antigens, potentially triggering an immune response against multiple cancer antigens simultaneously. However, challenges include the difficulty of mass-producing patient-specific cells and ensuring contaminant-free vaccine preparations [145,146,157-1159].

Tumor cell vaccines: Using multiple cell lines from various tumors in the vaccine formulation increases the likelihood that the patient's tumor shares antigens with the vaccine cells. This approach allows for a more generalized therapy, avoiding the need for individualized therapy for each patient. Despite promising results in inducing anti-tumor immunity, the clinical benefit of allogeneic tumor immunotherapies as monotherapies limited, possibly due to tumor-induced immunosuppression and tumor heterogeneity [160,161]. OncoVAX®, for instance, is a cellular vaccine used to treat advanced colon cancer, aiming to prevent cancer recurrence by activating the body's immune system using a patient's own cancer cells [162].

GVAX vaccines, which contain whole tumor cells genetically modified to produce the immune-stimulating cytokine GM-CSF (Granulocyte Macrophage Colony-Stimulating Factor), have shown immune responses and tumor regression in animal models but have had limited success in clinical trials for prostate cancer, melanoma, pancreatic cancer, and lung cancer [163]. Addressing the challenges of tumor heterogeneity and immunosuppression remains crucial for the development of effective cellular vaccines.

Immune cell cancer vaccines: Dendritic Cells (DCs) are essential for anti-tumor immune responses, easily isolated for CVs [164,165]. They excel at presenting antigens to T cells, activating them *via* signals like TCR and cytokines. DCs regulate T cell responses through cytokines, making them efficient in stimulating anti-tumor immune responses.

Research has focused on DC vaccines, where patient-derived autologous DCs are transfected with antigen genes or loaded with peptide antigen. This process involves obtaining autologous Peripheral Blood Mononuclear Cells (PBMCs) through apheresis, isolating DCs and/or monocytes using processes like Fluorescence-Activated Cell Sorting (FACS), and inducing differentiation into

dendritic cells [166,167]. Mature DCs express MHC I and II as well as co-stimulatory molecules after maturation, with antigen loading occurring after complete maturity, and patients receiving the mature antigens carried by DCs as a cellular vaccination [168,169].

Sipuleucel-T (Provenge), the first FDA-approved CV, treats metastatic castration-resistant prostate cancer (mCRPC) by enriching patient-derived DCs through leukapheresis and activating them *ex vivo* with GM-CSF fused to the antigen PAP (Prostatic Acid Phosphatase) [170,171]. While DC-based cancer vaccines effectively present tumor antigens to T cells, ineffective presentation can lead to tolerance and rapid tumor progression [172]. Other cell-based vaccines use bacteria or yeast to trigger an immune response or deliver tumor antigens [173].

The origin and development of virus-based cancer vaccines

Virus-based CVs use modified viruses to express tumor antigens, enhancing immune response [174,175]. OVs replicate in and kill tumor cells, releasing TAAs and activating the immune system [176,177]. OVs also target dysfunctional signaling pathways in cancer cells [178,179]. Some approved OV treatments include Rigvir, Oncorine, Imlygic, and Delytact for various cancers [180-182]. The heterologous prime-boost technique delivers a tumor antigen using one viral vector and boosts with another to overcome the antiviral immune response [183]. Directly injecting OV vaccines into tumors stimulates an anticancer immune response, benefiting "cold" tumors resistant to other treatments [184]. However, more research is needed to improve OV therapy for broader cancer types.

The origin and development of peptide-based cancer vaccines

Peptide-based CVs activate the adaptive immune response using epitope peptides to trigger responses against TAAs or TSAs [185-187]. They contain CD4+ epitopes for T-helper cell activation and CD8+ epitopes to CTLs *via* antigen cross-presentation. Short peptides (8-12 amino acids) directly bind to HLA (Human Leukocyte Antigen)/MHC class I on nucleated cells, enhancing anti-tumor immunity, but are HLA-type restricted. Synthetic Long Peptides (SLPs) (20+ amino acids) have wider HLA coverage and longer serum half-life, inducing potent and persistent antitumor immune responses involving CD4+ T cells, CD8+ T cells, and antibody production [188]. Peptide-conjugate vaccines combine peptides with adjuvants to activate DCs, while personalized peptide vaccines are customized to a person's neoantigen repertoire [189]. Despite challenges like tumor heterogeneity and immunosuppression, peptide-based CVs have significant potential to improve clinical outcomes and are actively researched worldwide. Combining them with other therapies can enhance their effectiveness, offering hope for cancer treatment advancements.

The origin and development of DNA-based cancer vaccines

They deliver genetic data encoding cancer antigens, prompting the body to produce antigen proteins and trigger an immune response against tumors [190-192]. DNA vaccines carry immunostimulatory or tumor antigen genes, stimulating the immune system [193]. DNA vaccines require transfection to produce antigenic peptides, entering the nucleus to transcribe mRNA and translate it into proteins recognized as foreign antigens by B- and T- lymphocytes. DNA vaccines can encode various tumor antigens, inducing humoral and cellular immunity and activating the innate immune response through pattern recognition receptors. However, they have weaker immunogenicity than mRNA vaccines, and strategies like codon optimization aim to enhance efficacy [194]. Therapeutic DNA vaccines raise concerns about antibiotic resistance due to their production using antibiotic selection markers [195]. Clinical studies show limited therapeutic success with DNA vaccines, attributed to tumor resistance mechanisms and the immunosuppressive TME [196]. Combining DNA vaccines with other therapies improves outcomes, suggesting future research should optimize their efficacy in specific cancer types and stages. Understanding the systemic effects of cancer and immune signatures of metastatic tumors could enhance DNA vaccination effectiveness. Identification of reliable cancer biomarkers as clinical endpoints and also use of DNA vaccines in combination with other treatments could become standard care for many cancers [190-196].

The origin and development of mRNA-based cancer vaccines

The emergency use of mRNA vaccines during the COVID-19 pandemic has shown their potential and opened new possibilities for mRNA therapeutics [197]. Compared to protein- and DNA-based drugs, mRNA vaccines offer advantages like direct encoding of multiple protein antigens and faster, more flexible, and less expensive production [198,199]. mRNA does not require nuclear entry for translation and has a short half-life, reducing the risk of insertional mutagenesis. These benefits have sparked interest in mRNA therapy for diseases such as cancer. Developing an mRNA vaccine against a tumor antigen involves synthesizing mRNA from a DNA template containing the antigen sequence. Modified nucleotides in mRNA synthesis can reduce immunogenicity and improve stability and translational efficiency. The 5'-cap structure and poly (A) tail are crucial for mRNA stability and translation. New components like circular RNA and Self-Amplifying RNA (SAM) show promise for enhancing mRNA vaccine efficacy [200]. The SAM platform, which uses positive single-stranded RNA viruses, can maximize antigen synthesis. Intramuscular mRNA Lipid Nanoparticle (LNP) vaccination is a promising delivery method due to its efficacy and ability to shield mRNA from degradation. Clinical development of mRNA vaccines for cancer is advanced, with vaccines encoding TAAs, TSAs, cytokines, and antibodies showing promise [201]. Challenges include improving mRNA stability, enhancing LNP-mediated mRNA delivery, and optimizing mRNA vaccine design for maximum immune response and minimal adverse effects [202,203]. Further research and comparisons of mRNA platforms are needed to advance mRNA cancer vaccines.

Combination Immunotherapy: Uniting Forces against Cancer?

The concept of using multiple immunotherapeutic strategies to treat cancer is rooted in the "cancer-immunity cycle," as proposed by Chen and Mellman in 2013 [204,205]. This cycle outlines the sequential steps of an immune response that targets cancer while mimicking the body's normal defense against foreign antigens. It begins with the presentation of TSAs, which are neoantigens resulting from genomic abnormalities like mutations or translocations, TAAs expressed in immune-privileged areas. APCs then migrate to secondary lymphoid organs, where they prime and activate naive T cells through MHC-antigen-T Cell Receptor (TCR) interactions and costimulatory signals. Activated T cells enter circulation, infiltrate the TME, recognize tumor cells *via* TCR-antigen-MHC interactions, and eliminate them. This process releases more tumor antigens, boosting the anti-cancer immune response. However, resistance mechanisms

can hinder each step, allowing cancer to evade immune destruction. Combining different immunotherapeutic approaches can potentially overcome these resistance mechanisms.

Combining immunotherapies to enhance cancer antigen presentation

Cancer cells often produce mutant proteins due to DNA mutations, leading to a high tumor mutational burden, which can predict response to immunotherapy [206]. However, patients with high mutational burdens may not benefit from immunotherapy if they cannot present cancer antigens effectively. Strategies that improve cancer antigen presentation, such as enhancing DC function and modifying the TME, can improve immunotherapy outcomes [207-209]. These strategies can include using DCs to present tumor antigens, modulating the TME with cytokines like interferon-α and GM-CSF, and employing immunostimulatory adjuvants to prime cytotoxic T cells. Additionally, targeting Myeloid-Derived Suppressor Cells (MDSCs) in the TME, which inhibit adaptive immune responses, could enhance immunotherapy efficacy. For example, targeting the chemokine receptor CXCR2 (C-X-C motif chemokine receptor 2) on MDSCs with mAbs has shown promise in inhibiting tumor growth and reducing MDSC recruitment [210,211]. Further research is needed to explore the potential of combining these immunotherapeutic approaches to improve cancer treatment.

Combinatorial immunotherapy to enhance immune response

Effective immune responses against tumors rely on priming and activating T cells in lymph nodes, followed by their migration to the TME to eliminate cancer cells [212]. CTLs play a crucial role in directly killing cancer cells, while CD4+ T Helper 1 (Th1) cells enhance T cell activation, CTL cytotoxicity, and the activity of other immune cells through cytokine secretion [213,214]. Negative feedback mechanisms, such as IL2/FOXP3-dependent pathways, can dampen T cell responses, limiting tumor cell killing [215]. Costimulatory molecules on activated APCs are essential for full T cell activation, and targeting inhibitory pathways, like coinhibitory receptors, can enhance CTL function [216,217]. Additionally, CD27 signaling is critical for optimal T cell priming and memory formation, and targeting the CD27/CD70 axis shows promise in reducing tumor growth and metastasis [218,219]. Agonistic antibodies targeting CD27 and CD40 have demonstrated efficacy in enhancing CTL responses and overcoming T cell tolerance in tumors [220,221]. Antibodies blocking CTLA-4, a co-inhibitory molecule, can enhance anti-tumor immunity [222]. Combinatorial immunotherapy that targets these immune escape mechanisms holds potential for improving cancer treatment efficacy [223,224].

Enhancing immune cell infiltration in cancer: A combined immunotherapy approach and its challenges

Combinatorial immunotherapeutic approaches aim to enhance immune cell access to cancer cells, critical for tumor growth and metastasis. Immune cell infiltration relies on migration and is regulated by chemokines [225,226]. Dysregulation can hinder recruitment, necessitating combination therapies like CAR-T cells and BiTEs (Bispecific T-Cell Engagers) for effective tumor immunotherapy [227,228]. Successful immune-mediated tumor eradication requires immune cell penetration into tumors and identification of malignant cells [229]. Effector T cells penetrate some solid tumors, but the immunosuppressive TME hampers their potential. Modulating tumor vasculature can enhance immune cell penetration and tumor oxygenation, counteracting TME immunosuppression. Targeting CAMs (Cell Adhesion Molecules) and combining ICTs with VEGF (Vascular Endothelial Growth Factor) inhibitors may enhance immunotherapy efficacy, with tumor vasculature normalization potentially becoming standard in solid malignancy treatment [230,231].

Lastly, combination immunotherapy aims to enhance cancer cell recognition and kill by addressing various immune evasion mechanisms. Cancer cells can evade immune recognition by modifying MHC molecules or producing immunosuppressive factors [232]. Strategies to counter this include re-directing innate immunity, using mAbs to enhance antigen presentation, and inhibiting immunosuppressive enzymes like IDO1 (Indoleamine 2,3-Dioxygenase 1) [233,234]. Despite these advances, inter-patient heterogeneity remains a challenge in developing effective combination therapies [235]. Additionally, targeting and killing cancer cells can be hindered by low immunogenicity due to synonymous mutations [236-241]. Understanding the complexity of Tumor-Associated Macrophages (TAMs) and utilizing approaches like immunomodulation and OVs can enhance the effectiveness of combination immunotherapy [175,176,208-210]. Numerous immunotherapeutic approaches are being explored in clinical trials, highlighting the evolving landscape of cancer treatment [87-90].

Conclusion and Future Directions

Cancer vaccines, hailed as a potential breakthrough in cancer treatment, have demonstrated the ability to stimulate the immune system against tumors. However, they encounter significant challenges in achieving widespread clinical efficacy. One key obstacle is the selection of appropriate tumor antigens. The identification of antigens specific to cancer cells, while avoiding those also present in healthy tissues, is crucial for an effective immune response.

Furthermore, immune tolerance mechanisms can weaken the immune system's reaction to cancer cells, diminishing the vaccines' effectiveness. The immunosuppressive TME, characterized by factors such as Tregs and MDSCs, further impedes the immune response triggered by vaccines. As standalone treatments, CVs have limitations. Nonetheless, when combined with existing immunotherapies like immune checkpoint inhibitors, their efficacy can be boosted. This combined approach has shown promise in clinical trials and is being actively investigated as a treatment strategy.

Cancer immunotherapy, including vaccines, was named the "Breakthrough of the Year" in 2013, underscoring its potential to revolutionize cancer treatment. The success of mRNA vaccines during the COVID-19 pandemic has renewed interest in CV development, with researchers exploring novel approaches to enhance their efficacy. Future research in CV development should prioritize several key areas. One critical aspect is the identification of effective tumor antigens. Machine learning and AI (Artificial Intelligence) can play a significant role in analyzing vast datasets to identify the most promising antigens for vaccine development.

Understanding Cancer Stem Cells (CSCs), which are thought to drive tumor growth and resistance to therapy, is crucial for developing more precise vaccines. Identifying the unique immune characteristics of CSCs that set them apart from other cancer cells is essential for generating an effective immune response against them using CVs. Targeting these cells has the potential to prevent tumor recurrence and enhance long-term patient outcomes.

Advancements in sequencing technologies and bioinformatics are transforming cancer treatment, enabling personalized immunotherapies. By analyzing the genetic makeup of individual tumors, treatments can be tailored to target specific mutations or molecular pathways, enhancing their effectiveness. For example, identifying mutations that make tumors susceptible to ICTs allows for more precise treatment selection, improving response rates. Additionally, sequencing helps identify tumor antigens, guiding the development of vaccines or ACTs that stimulates the immune system to target cancer cells specifically. These advancements hold promise for improving cancer treatment outcomes through targeted and personalized approaches. Another critical area for research involves enhancing our understanding of the TME and its impact on immune responses. By identifying strategies to modulate the TME to favor an anti-cancer immune response, we can enhance the effectiveness of CVs and other immunotherapies.

To conclude, notwithstanding the obstacles that CVs must overcome, including the strategies of evasion that cancer cells use and the unpredictability of patient reactions, they remain a potential means of battling cancer. The field's continuous investigation and progress, propelled by discoveries in immunology, genetic engineering, and personalized medicine, provide invaluable perspectives for transforming cancer therapy methodologies. Utilizing the body's immune system to target and eliminate cancer cells, these vaccines hold promise for treating cancer with greater precision and minimal invasiveness, while also potentially preventing cancer recurrence. The idea of customized cancer vaccinations based on a person's genetic profile and tumor features is becoming increasingly important as researchers continue to explore the intricacies of cancer biology and improve vaccine creation methods. CVs appear as a ray of hope for revolutionary change in oncology, promising improved patient outcomes and a more promising future in the battle against cancer, thanks to coordinated efforts across multiple scientific disciplines and a devoted pursuit of novel therapeutic techniques.

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