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FROM RISK TO QUALITY: QUALITY RISK MANAGEMENT IN PHARMA TARGETING CANCER THROUGH IMMUNE MODULATION

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Abstract

Cancer immunotherapy has emerged as a powerful strategy for treating cancer by enhancing the body's own immune system to recognize and eliminate tumor cells. Both experimental and clinically approved therapies are being developed to improve treatment outcomes and achieve long-term tumor control. Several factors influence the effectiveness of immunotherapy, including tumor heterogeneity, gut microbiota composition, genomic variations, and epigenetic modifications. Understanding these factors helps researchers design more precise and personalized treatment approaches. A major focus of current research is the study of molecular mechanisms behind immune evasion and therapeutic resistance. Noncoding RNAs and epigenetic alterations play significant roles in regulating immune responses and tumor progression, making them promising targets for innovative intervention strategies. Various immunotherapy platforms, such as immune checkpoint inhibitors and other immune-based technologies, are being investigated and implemented in clinical practice to improve patient outcomes.

Keywords: *Microenvironment remodeling, Cancer vaccine, cancer, chimeric antigen receptor-T cells, immune check point, cancer, immunotherapy, antibodies.*

1. INTRODUCTION

It is projected that there would be 618,120 cancer-related fatalities and 2,041,910 new cancer cases in the US alone by 2025. Approximately 2.5 times as many people are anticipated to die from lung cancer as from colorectal cancer (CRC), which has the second-highest mortality rate. Breast cancer is expected to be the most common cancer diagnosed in women, while prostate cancer is predicted to be the highest prevalence in men [1]. Cancer immunotherapy, which involves using the immune system to fight cancer, is one of the most successful cancer prevention techniques. This strategy uses immune cells or immune system modulation to prevent the growth of tumors. [2]. The immune system was thought to be one of the possible causes of tumor regression at this time [3,4]. Improvements in molecular biology and immunology during the 20th century made immunotherapy a ground-breaking area of medicine. While monoclonal antibodies made it possible to precisely target particular antigens, discoveries like cytokines, such as interleukins and interferons, demonstrated the significance of important molecules in controlling immune responses. [5]

2. HISTORY OF CANCER IMMUNOTHERAPY

The immune system's capacity to identify tumor antigens and affect the development of cancer within the TME is the foundation of immunotherapy, a method of treating cancer. Prior to exploring the processes, contemporary uses, and therapeutic approaches of cancer immunotherapy, it is essential to comprehend its historical history. Observations of an elevated cancer risk in immunocompromised patients gave rise to the idea of cancer immunotherapy. Tumor regression and growth suppression have been observed since the 1700s, and in the late 18th century, histological investigations offered scientific explanation. German researchers Busch and others separately noted tumor suppression in erysipelas infected patients about 140 years ago [6].

1. Basic Concept And Key Steps

Key steps in immunity to achieve effective cancer immunotherapy, multiple steps must be either naturally or by means of therapy, to improve immune monitoring. By digesting tumor antigens, DCs are

essential for starting cancer immunotherapy. These tumor antigens, which are protein changes commonly linked to tumors or non-mutated genes produced by cancer cells, can have a local origin or be introduced by vaccinations. DCs must have a strong enough interaction with tumor antigens to collect and present antigens efficiently. [7]

3. CANCER IMMUNOTHERAPIES

Maintaining the integrity of our health is mostly dependent on our immune system. In addition to its well-known function in defense against infections, it plays a less noticeable but equally important part in the prevention and defense against cancer. Paul Ehrlich made the hypothesis that cancer may be controlled by using the immune system's strength as early as 1909. [8].

4. PASSIVE IMMUNOTHERAPIES

Immunosuppressive factors make it difficult for many patients to mount a healthy anti-tumor immune response. Therefore, passive immunotherapies aim to combat cancer directly in order to get around this restriction. These substances have trinsicanti humoral properties and have the ability to either directly or indirectly target tumor cells. These kinds of molecules will be further described in this section [9].

a. Cytokines

Both inflammatory and non-inflammatory cells express cytokines, which are tiny chemicals that help regulate inflammation and other immune responses. These compounds have been given to cancer patients in an attempt to unspecific ally boost anti-cancer immune responses. Granulocyte and macrophage colony stimulating factor (GM-CSF) and interleukin-2 (IL-2) are the two primary cytokines that will be covered [10].

b. Antibody Therapy

One of the most effective forms of treatment for solid and hematologicaltumors in the clinic is antibody therapy for cancer. Since they were initially identified as chemicals that neutralize diphtheria in 1890, antibodies have advanced in cancer treatment (Behring, 2013). Later, it was discovered that these compounds were secreted by our own cells, namely in certain plasma B cells, and that they possessed a particular property in detecting particular epitopes (Farage us, 1947; Van Epps, 2005) [11].

C. Active Immunotherapy

Active immunotherapies are chemicals that are utilized to stimulate or restore anti-tumor responses in vivo, as opposed to passive immunotherapies. For treatment to be effective, patients' immune systems must be receptive and active [12].

D. Checkpoint Inhibitory Therapy

T cells start their lives in the thymus by multiplying and producing a wide variety of TCRs. The immune system must be able to differentiate between self and non-self in order to preserve homeostasis. Central tolerance is the first selection phase that T-cells go through. T-cells that respond aggressively to self-peptides that are provided by the myocytes go through apoptosis throughout this phase. Weakly responding T-cells to self-peptides are discharged into secondary lymphoid organs as naive cells [13].

d. PD1/PD-L1 axis

PD-1 belongs to the CD28/B7 family of costimulatory receptors, just like CTLA-4. It binds to its ligands, PD-L1 and PD-L2, which are expressed by both hematopoietic and non-hematopoietic cells, and regulates effector T cells (Figure 6). Both PD-1's immunoreceptor tyrosine-based inhibitory motif (ITIM) and intracellular immune or receptor tyrosine-based switch motif (ITSM) become phosphorylated during activation [14].

e. Cancer Vaccines

One significant advancement in the fight against infectious illnesses that can be fatal is the development of vaccines. The idea of triggering an immune response that creates a memory that protects against cancer is excellent. This might aid with tumor recurrence in addition to preventing or treating cancer. Nevertheless, since the majority of the tumor antigens that are strongly expressed on tumors are also shared by healthy cells, cancer genomics has demonstrated the difficulty in accomplishing this. Despite being expressed on healthy tissue, TAAs including HER2, glycoprotein (gap) 100, Telomerase, and others are perfect antigen candidates because of their immunogenic qualities (Finn, 2018; Blass and Tot, 2021). This lack of specificity is concerning due to the "off-target" effects that can be very toxic to a patient However, the FDA authorized Sipuleucel-T, the first therapeutic cancer vaccine, in 2010 for metastatic prostate cancer that was asymptomatic or just minimally symptomatic (Plusher, 2011). Prostatic acid phosphatase (PAP), a well-known TAA, was used to grow and activate dendritic cells that were isolated from the patient's PBMCs ex vivo. The licensure of this type of cancer vaccination encouraged more vaccine platforms to be studied in clinical settings. For instance, Five, a new RNA lipoplex complex that codes for several TAAs, was created by Bison Tec (Shin et al., 2020). Such platform scan selectively targets dendritic cells to induce an appropriate antigen presentation allowing for an effective T-cell immune response [15].

5. CANCER IMMUNOTHERAPY STRATEGIES

Oncolytic virus therapy Basics

It has been studied to utilize viruses as experimental agents to cause cell death or dysregulation. Oncolytic viruses (OVs) were developed as a result of the introduction of the idea of employing viruses to eradicate cancer cells in the 1990s. Within cancer cells, OVs multiply and cause immunogenic cell death (ICD) and lysis. Many OVs are currently undergoing preclinical research, even if others, like T-VEC, have been approved by the Food and Drug Administration (FDA) for clinical usage. The inability of gene therapy

vectors to multiply inside infected cells is what separates OVs from gene therapy. There are two types of OVs: genetically engineered and naturally occurring. The first OV, T-VEC, was authorized by the FDA in 2015 to treat metastatic melanoma's- The oncolytic herpes simplex virus type 1 (ohms'-1) is the basis for VEC, which has undergone a number of genetic changes to increase its oncolytic efficacy. In 2021, Japan also authorized DELYTACT (ohms'-1 withG47Δ), the first targeting glioblastoma. OVs may be modified to express transgenes that work via four different mechanisms: oncolytic, vascular collapse, anticancer immune response, and the production of therapeutic transgenes to limit tumor development. OVs are utilized for the targeted therapy of cancer cells [16].

6. IMMUNE CELL ENGAGERS

Improvements in molecular biology and immunology over the 20th century made immunotherapy a ground-breaking area of medicine. While monoclonal antibodies made it possible to precisely target a particular titan, discoveries like cytokines, such as interleukins and interferons, demonstrated the significance of important molecules in controlling immune responses. Additionally, the introduction of immune checkpoint inhibitors transformed cancer therapy paradigms, and the identification of immune checkpoint proteins such as CTLA-4 and PD-1 revealed crucial routes by which cancer cells elude immune monitoring. The goal of Immune Cell Engagers (ICEs), which are molecule-based treatments, is to activate immune cells to target cancer cells in order to overcome immune evasion and reroute immune cells for increased anti-tumor action [17].

a.T CELL ENGAGERS (TCES)

The problem of tumor cells downregulating MHC expression, a typical immune evasion strategy that impairs T-cell-mediated anticancer activity, is addressed by TCEs, which are bispecific antibody-based treatments. By directly targeting the tumor-associated antigens (TAAs) on cancer cells and the T-cell receptor or CD3 complex on Tells, these treatments work through MHCindependent pathways. When T cells are activated by this binding, performing and gran enzymes are released, which destroy tumor cells. Transpacific TCEs with extra characteristics to improve T-cell activation and half-life-extended TCEs that employ Fc domains to lengthen circulation time in vivo are examples of advanced TCE platforms [18].

b. NK CELL ENGAGERS (NKCES)

NKCEs are a new family of immunotherapeutic drugs that target cancer by using natural killer (NK) cells' intrinsic immunological capabilities. Through the activation of receptors such as CD16 (Face RIII), NKG2D, or NKp30, NKCE enhances NK cell-mediated cytotoxicity by connecting NK cells to tumor-associated antigens (TAAs) including HER2, CD19, or BCMA. [19]. Phagocyte ENGAGERS (PCES)

PCEs are immunotherapeutic strategies that activate phagocytes such as macrophages and dendritic cells to eliminate tumor cells. These therapies use the innate immune system's natural capacity for tumor clearance while counteracting immune evasion tactics used by cancer cells. A defining feature of PCEs is their ability to connect phagocyte directly to tumor cells, inducing antibody-dependent cellular phagocytosis or stimulating inflammatory responses. One of the key mechanisms of PCEs involves targeting the CD47-SIRPα axis. Tumor cells frequently overexpress CD47, a "Don't Eat Me" signal that binds to SIRPα on macrophages, inhibiting phagocytosis (Figure 6). Blocking this interaction restores macrophage-mediated clearance of tumor cells, enhances antigen presentation, and shifts tumor-associated macrophages from an immunosuppressive M2phenotype to a pro-inflammatory M1 phenotype, boosting antitumor immunities are useful in both solid and hematologic malignancies because they work as bispecific antibodies that target certain tumor antigens or as antigen-dependent agents that alter the tumor microenvironment [20].

4. NEW DEVELOPMENTS IN CANCER IMMUNOTHERAPY

Significant progress has been achieved in improving the specificity of the T-cell receptor (TCR) or by introducing antibody-like recognition domains in the form of chimeric antigen receptors (CARs). Tumors employ a number of strategies to avoid the host immune response, including but not limited to inducing energy (unresponsiveness) in T cells, releasing immune-suppressive cytokines, and using local mediators to change the tumor environment. These strategies are encouraging and have been successfully demonstrated using engineered T-cells. T-cells are essential for cell-mediated immunity, and more recently, methods to genetically modify T cells have been used to treat B-cell lymphomas by changing CAR T-cells (CAR-T). The increasing number of people using this technology is a reflection of its therapeutic successive time, tumor cells develop strategies to evade immune monitoring, primarily from the immunological response mediated by T cells. This is the main tactic used in immunotherapy to target immunological checkpoint modulators. The actions of T cells can be either stimulated or inhibited by antibodies that block these immune-modulatory proteins [21].

8. TUMOR-INFILTRATING LYMPHOCYTES

Because immunotherapy has shown remarkable results in patients with solid tumors and chemotherapy-refractory acute leukemia, it has created a great deal of optimism for cancer treatment. The majority of immunotherapeutic approaches work by stimulating the T-cell response to combat cancer. Using an antibody that is specific to both T cells and malignancies, known as a bi-specific antibody, or inhibiting T-cell suppression signals, which are mostly mediated by T regulatory cells, can both stop the

spread of cancer. Adoptive T-cell treatments include isolating and manipulating a patient's T cells in a lab before reintroducing them [22].

9. ADVERSE EFFECTS OF CANCER IMMUNOTHERAPY [23].

- Cancer immunotherapy improves the efficacy of treatment by strengthening the immune system's capacity to identify and destroy cancer cells. Pneumonitis, endocrinopathies, gastrointestinal toxicity, and systemic inflammation are just a few of the serious side effects that it might cause...
- There have also been reports of rare but dangerous toxicities, such as renal failure, neurological conditions including encephalitis and neuropathies, and cardiovascular problems like myocarditis.
- In addition to increasing T-cell responses against malignancies, ICIs may cause I rates, some of which are controllable and well tolerated.

10. FUTURE PROSPECTS

The research can be advanced in a number of encouraging ways. It is possible to improve personalized medical approaches, which will enable the creation and use of customized treatments based on each patient's unique immune profile and tumor features. Although factors like efficacy, [24] long-term biosafety, and scale ability for large-scale manufacturing are still important, nanoscale delivery technologies have also been emphasized as a way to greatly increase the effectiveness of cancer immunotherapy. [25] As the impact of the gut microbiota on the results of cancer immunotherapy becomes more widely acknowledged, altering the makeup of the gut microbiota offers a viable tactic to enhance treatment outcomes. Changing immunologically "cold" cancers into "hot" ones may make them more vulnerable to immunotherapy and enhance the efficacy of treatment. There is a lot of promise for improving response forecasts and advancing customized treatment with the incorporation of AI into cancer immunotherapy [26].

11. CONCLUSION

Cancer immunotherapy has emerged as a highly promising and rapidly advancing approach in modern oncology, offering improved survival outcomes and enhanced quality of life for many cancer patients. It includes a wide range of treatment strategies such as targeted monoclonal antibodies, cancer vaccines, adoptive cell therapies (including CAR-T), oncolytic viruses, checkpoint inhibitors, immune cell engagers, and cytokine-based therapies. These therapies can be used as stand-alone treatments or in combination with conventional options such as surgery, chemotherapy, radiotherapy, and targeted therapy to increase overall treatment effectiveness. Compared to traditional cancer treatments, immunotherapy may also produce different and sometimes fewer side effects, although responses vary depending on the patient and cancer type. However, despite its clinical success, cancer immunotherapy is not universally effective because cancer is highly heterogeneous and treatment responses differ among individuals.

11. AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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None

13. DECLARTION COMPETING INTEREST

The authors have no conflicts of interest to declare.

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