Cancer Immunotherapy: A Brief History, The Latest Development of Typical Subtypes and Therapy Combination

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Abstract. The leading cause of death in humans has long been considered cancer. People have developed a variety of cancer treatments as science has advanced. However, the side effects and flaws of the therapies are still intolerable for patients. Cancer immunotherapy, which potentially can give a long-lasting treatment with minimal toxicities, finally appeared to address the inadequacies. Cancer immunotherapy keeps up with the advancements in contemporary health. In recent years, there have been many updates on the many subtypes of cancer immunotherapy. A brief history of cancer immunotherapy and the most current developments are summarized in this paper. The assessment also emphasizes the newest investment trend in cancer immunotherapy and prospective drug combinations.

Keywords: Cancer Immunotherapy; History of Cancer Immunology; Monoclonal Antibodies; Cancer Vaccines; STAT3; Wnt/ β -catenin Signaling Pathway.

1. Introduction:

According to the definition provided by the World Health Organization, cancer is a broad term for a collection of disorders that are characterized by uncontrollably growing cells that resist the body's natural processes of elimination, infiltrate nearby organs, and spread to other organs. During the battle between cancer cells and the human body, cancer may create tumor antigens as it progresses, making it easier for the immune system to trigger an immunological response[1, 2]. It is crucial and potent for the immune system to successfully eradicate aberrant cells with genetic mutations [3]. The innate and adaptive immune systems may participate in the process[4, 5]. Natural killer cells, eosinophils, basophils, and phagocytic cells, particularly mast cells, neutrophils, monocytes, macrophages, and dendritic cells (DCs), make up the innate immune system[6, 7]. B cells and T cells are examples of lymphocytes that the adaptive immune system will use. Both the innate immune system and the adaptive immune system are heavily involved in the removal of tumors [8]. The phenotypic may be harmed, and tumor cells may be eliminated by immunoreaction[8]. More importantly, immune responses to tumor cells can target specific cancer cells precisely. Most cancer cells inside the body are destroyed by innate and adaptive immunity, especially natural killer (NK) cells[9]. TNF- and IFN-, two proinflammatory cytokines released by NK and Type 1 Helper T cells, direct monocytes to become immunostimulatory macrophages that phagocytize cancer cells.[10]. Additionally, interleukin-12, secreted by active macrophages, can promote the growth and activation of T cells to enhance adaptive immunity.[11].Finally, the trained memory T cells can target cancer cells and eradicate them for a considerable time.[12]. For this reason, researchers are hopeful that immunotherapy will be effective in the fight against cancer.

To defeat each immune system component, cancer cells may evolve various resistance strategies, such as local immune evasion, induction of tolerance, and deceptive T celT-cellaling, to avoid being eliminated by the immune system[8, 13, 14]. And after years of research, scientists have uncovered the key ways tumor cells avoid immune systems' inhibition. And for the same reason, modern cancer treatments require the employment of additional techniques like surgery, radiation, and chemotherapy to make up for the immune system's deficiencies. Therefore, researchers have concentrated on making discoveries that could boost immune systems' built-in defenses.

Nearly a century ago, the concept of enhancing immune systems to combat diseases first emerged. The development of immunotherapy is a tale of human understanding. During decades of research, scientists have developed a few methods to activate immune systems, including activating effector

mechanisms to combat inhibitory and suppressive mechanisms[15, 16]. Clonal antibodies, cancer vaccinations, and regulatory T-cell reduction are among the most widely used approaches. And perhaps more crucially, scientists now understand how tumor cells control immune cells and avoid being destroyed by immune systems as a result of in-depth research. Several intracellular signaling pathways are typically dysregulated by cancer cells to change the surroundings both within and outside of the cells, particularly the tumor microenvironment (TME)[17].

This review provides a brief overview of the history of immunotherapy, summarizes recent advancements in cancer immunotherapy based on different subtypes of treatment, and focuses on the effectiveness of recent clinical trials using a combination of standard cancer immunotherapy drugs and relative signaling-pathway inhibitors.

2. A Start of Cancer Immunotherapy:

Ancient Egypt is the origin of the oldest cancer immunotherapy. Nearly 3000 years ago, numerous instances of tumor elimination following infection and concurrently high fever were documented. Galen, a Greek doctor, attempted to explain the resemblance and connection between tumors and inflammation.[18, 19]. However, it wasn't until the late 18th century that histologic confirmation of malignant tumors allowed researchers to begin considering the potential of employing the immune system to fight the malignancy. The most well-known instances of contemporary cancer immunotherapy were first documented separately by two German doctors, Busch and Fehleisen, about 150 years ago[18]. The two both noticed regression of tumors happened in patients after accidenerysipelas infections ions[20]. When Busch attempted to spread erysipelas to a cancer patient in 1868, the tumor shrank. After conducting the experiment again, Fehleisen concluded that Streptococcus pyogenes was the source of the erysipelas[20]. However, neither of them ultimately saws many successes with tumor therapy.

Then, in 1891, a significant development occurred when William Bradley Coley, regarded today as the Father of Immunotherapy, followed up on an independent finding of long-term sarcoma remission following erysipelas infections.[18, 21]. Coley concluded that over 47 cases of patients with incurable tumors experienced spontaneous remission following acute bacterial infections after further examination of earlier records and literature. He initially explored using the immune system to treat bone cancer. Then he experimented with injecting heat-inactivated germs into cancer patients to stimulate their immune systems to fight sarcomas. He applied his solution therapy to a variety of cancers, such as testicular carcinoma, sarcoma, and lymphoma. He listed nearly a thousand instances of tumor regressions. But because Coley's approach lacked a consistent and repeatable level of therapeutic efficacy, it was not given due consideration.[18, 21].

In 1945, interest in immunotherapy began to pick up again, which led to many developments in the field of cancer immune therapy.[22], such as interferon[23] and the first cancer vaccine designed by Ruth and John Grahams[24]. Scientists have gained a deeper understanding of immune cells over time, including their existence and fundamental roles. For example, T cells were identified by Jacques Miller in 1967[25], dendritic cells were discovered by Steinman in 1973[26], and following closely natural killer cells (NK cells) were described by Klein in 1975[27]. Meanwhile, important scientists and doctors from the University of Minnesota used earlier knowledge to develop the bone marrow transplantation for hematological tumors procedure that is being used today.[28].

Immunotherapy gained significant scientific attention after being restarted. As knowledge of the immune system increased, researchers started to use the pertinent information, helping the development of later cancer immunotherapy. For instance, research on antibody-based treatments grew in the decades that followed the discovery of antibodies by Paul Ehrlich, Emil von Behring, and Kitasato Shibasaburo in 1890[18]. This research eventually resulted in the development of rituximab, a monoclonal antibody that binds to the CD20 protein that is present on the surface of immature B cells[29]. In 1997 Rituximab was the first monoclonal antibody approved by the The United States Food and Drug Administration (FDA) for the treatment of non-Hodgkin's lymphoma[29]. As with

monoclonal antibodies, there are many subcategories of cancer immunotherapy, including cytokines, immunosuppression reduction, cancer vaccines, and adoptive cell treatment. The review will follow each immunotherapy subtype's most recent discoveries in the part after that. **[Figure 1, [30]]**

3. The Latest Development in Cancer Immunotherapy:

3.1 Monoclonal Antibodies (mAbs)

These are immunosystem protein replicas created by humans. Because they may be created to target the antigens found on the surface of cancer cells, mAbs can be highly effective in the treatment of cancer. The effector mechanism of mAb is primarily based on two dimensions: directly blocking growth factor receptor signaling or working in conjunction with the immune system of the host, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP). Additionally, the majority of targeted mAbs have the ability to stimulate the complement system. The first mAb was created in a laboratory by Milstein and Köhler in the 1970s.[30]. The study and creation of mAbs flourished for many years after that. Many well-known mAbs were created in following years, such as rituximab, trastuzumab [31], and pertuzumab [32]. At the beginning of the mAb study, the main focus was on improving the cytotoxic impact on cancer cells. However, with the significant advancements achieved in recent years, the effector mechanism of mAb has changed to utilize immune cells to increase their anti-tumor capacity. Not to mention that its most well-known and optimistic discovery, the inhibition of immunological checkpoints, will be covered in the subsequent section.[33]. In recent 2 years, like disitamab vedotin, tisotumab vedotin, naxitamab, and margetuximab[34-37], the number of mAbs that the FDA has approved has greatly increased. However, a notable drawback of earlier mAbs was their potential to select for tumor cells. Meanwhile, mAbs may lead to cancer cell mutation, encourage the malignancy of other cancer cells, and enhance the development of acquired resistance to medication.[38]. Scientists nowadays are focusing on finding a solution to the issue. In order to reverse resistance to cetuximab without changing the binding epitope or impairing antibody function, Chinese researchers developed a structure-guided and phage-assisted evolution strategy in 2022[39].

3.2 Non-specific Immunotherapies

I. Cytokines

Cytokines are small proteins that the immune system's various immune cells naturally make and emit. They are essential for adjusting immune system activation and serving as signaling molecules in the immune system[40]. This form of non-specific immunotherapies might be created and found inside bodies, unlike other non-specific immunotherapies. The first cytokine to be FDA-approved for the treatment of advanced melanoma and metastatic renal cell carcinoma was IL-2[41]. NK cells, CD8+ cells, mast cells, and dendritic cells all generate IL-2 in the human body. IL-2's ability to promote T cell proliferation, differentiation, and activation serves as the basis for the mechanism through which it works in cancer treatment. IL-2 can encourage NK cells to boost cytolytic activity.[42]. The use of IFN-γ was also authorized to treat a number of human malignancies[43]. Like IL-2, IFN-γ is produced by T cells and NK cells. However, cytokines as a treatment still have issues. One explanation is because the function of cytokines in the immune system is still poorly understood. The other factor that prevents cytokines from being used clinically is that they have a short half-life in vivo and significant toxicity at therapeutic levels[44]. The most recent advancements in cytokine research focus on lowering toxicity and enhancing the anticancer effectiveness of systemically administered cytokine medicines. Scientists are working to strike a balance between peripheral toxicity and cytokine activation. Making cytokine prodrugs with blocking polypeptides to achieve low toxicity is one potential remedy[45]. In the meanwhile, scientists are working to create personalized pro-cytokines to better effectively treat each type of tumor[46].

II. Immune checkpoint inhibitors (ICI)

Immune checkpoints are crucial areas where the immune system must check that the immune response is appropriately triggered. These checkpoints work by controlling the T cell receptors and receptor-bindings in the surrounding microenvironment[47]. In mice infected with a chronically persistent strain of the lymphocytic choriomeningitis virus in 1998, the immunological checkpoints' mechanism was uncovered[48]. Scientists have found plenty of checkpoint molecule pairs, containing co-stimulatory and co-inhibitory, for example, CTLA-4/B7[49], PD1/PDL-1[50],TIGIT/ CD155 [51], LAG-3/ MHCII[52] and TIM3/Gal-9[53] [**Figure 2, [54]**]. The most well-known of these pairings must be PD1/PDL-1, which is why Professor Honjo received the 2018 Nobel Prize in Physiology for his work on this combination. Immune tolerance in TME is induced and maintained under the direction of the PD-1/PDL-1 pathway. T cell activation and anti-tumor responses will be regulated by the pair's activities.[55]. As early as 1987, CTLA-4 was reported that it could be expressed on activated effector T-cells and regulatory T-cells[56]. Leach, Krummel, and Allison reported in 1996 that mAbs blocking CTLA-4 might cure malignancies in animal models[57]. ICI can more readily be manufactured and target T cells to guide an immune response against tumor cells. ICI has so garnered a lot of interest. ICIs that target PD-1/PD-L1 and CTLA-4 have become a mainstay in the treatment of cancer. The response rate to ICIs is still poor in the interim. In contrast to CTLA-4 inhibitors, PD1 inhibitors like Pembrolizumab and Nivolumab have demonstrated better efficacy[58].

However, in comparison to other cancer therapy, the response rates are quite low. These concerns are being addressed by researchers. To boost effectiveness, they first look for interaction between various cell death pathways and antitumor immunity[59]. Second, they are examining the inhibitory targets that indirectly control T cells, such CEACAM[60], CCL2/CCR2[61], LIF[62], and CD47/SIRPα[63]. Finally, to increase therapeutic effectiveness, scientists aim to combine ICIs with signaling pathway inhibitors. Moreover, the latest trend of mAb usage is Combination Therapies, peculiarly the combination of multiple subtypes of mAbs. For example, In the section after this, we'll explain this aspect in more depth.

3.3 Cancer Vaccines

Scientists have endeavored to utilize vaccinations to destroy tumor cells in the same way that they protect individuals from dangerous viruses and bacteria with conventional vaccines. The hepatitis B (HBV) vaccination and the human papillomavirus (HPV) vaccine are two cancer vaccines that the FDA has licensed in past years for the prevention of certain malignancies[64], which are correlated with tumorigenesis directly. The HPV vaccination is often used as an example to explain how this type of cancer vaccine works to prevent cancer based on a variety of impacts. The HPV vaccination can cause systemic antibodies, mostly immunoglobulin (Ig) G, as well as reactions from both B cells and T cells. The HPV vaccine works primarily through IgG to protect against HPV infections, which can exude at the areas of trauma.[65]. But in addition to developing cancer vaccinations that initially work to stave off viral infections, scientists have also worked to create cancer vaccines that can treat already-existing malignancies. Producing customized cancer vaccines using patient cells is the first tactic[66]. In the early 1970s, it was the first time for researchers to produce this kind of cancer vaccine for melanoma[67]. The allogenic vaccine, which is created using lab cell lines, is the second form of cancer vaccination[68]. Therefore, this type of vaccination specifically targets nucleic acids, proteins, and peptides in cancer cells. This will make production more challenging but might result in cheaper manufacturing costs. Because they are simple to produce, peptide- and protein-based vaccinations are now the focus of scientific study. Many clinical studies based on these cancer vaccines are now being conducted, including those using Sipuleucel-T, Talimogene Laherparepvec, CMB305, and Belagenpumatucel-L[69-72]. Due to a significant clinical study finding, it has been established that cancer vaccines would have effective curative effectiveness.

4. Intrinsic Signaling Pathways Performing in Cancer Immunology

The current limitation of cancer immunology, as previously indicated, is that each kind of cancer immunotherapy only works in a small number of patients. A reduction in efficient immune cell infiltration and an expansion of immunosuppressive cells in the TME are two components of a potential mechanism for immunotherapy resistance[73]. While this is happening, the effectiveness of passive curative therapy is influenced by the variety of people and tumor types[74]. The phenomena led researchers to hypothesize that the key mechanism may be variations in somatic mutations among tumors, which were primarily brought on by varying activation of certain tumor-intrinsic pathways. With future research, it may be possible to control the immunosuppressive TME and facilitate tumor immune escape by activating signaling pathways inside tumor cells[75]. Here are two typical pathways involving immunosuppression and oncogenesis:

4.1 Wnt/β-Catenin Signaling

Wnt signaling dysregulation and aberrant expression are linked to a variety of illnesses, such as cancer, osteoarthritis, asthma, allergy, and autoimmune disorders[76]. Recent studies confirmed the relationship between immune cells, particularly cancer immune microenvironments, and Wnt signaling and Wnt ligand[77]. T-cell infiltration, which is the primary method of self-elimination in malignancies and immunotherapy, can be influenced by Wnt/-Catenin signaling[78]. Wnt ligands may interact with dendritic cell FZD receptors to promote the inhibition of CTLA-4, PD-1/PD-L1, and immunological suppression[79]. In order to boost the immunosuppressive effect on Treg cells, Wnt signaling is also capable of promoting the production of immunosuppressive cytokines including IL-10 and TGF-β[80]. Wnt signaling activation may enhance initial resistance to immunotherapy, according to recent studies[81]. Immune checkpoint inhibitors combined with Wnt signaling inhibitors that target various Wnt pathway mediators or ligands have been used in several clinical studies and have demonstrated therapeutic effectiveness[82].

4.2 STAT3 Signaling

STAT3 is a member of the mammalian STAT family, which also includes STAT1, 2, 3, 4, 5a, 5b, and 6[83]. In most human malignancies, STAT3 is abnormally hyperactivated and is typically associated with passive survival outcomes[84]. It has been demonstrated that STAT3 can drive tumor immunosuppression at a variety of levels, including the inside of the tumor cells, immune cells, cancer-associated fibroblasts (CAFs), and TME[84]. STAT3 promotes the production of immune-suppressive genes from within tumor cells[85]. Additionally, cancer cells can be helped to suppress the production of immune-stimulating molecules including IL-12 and CCL5[86], and upregulating the expression of immune suppressants such IL-10 and TGF-β[87].Through the p300-mediated acetylation and production of CXCL12, STAT3 can interact with the NF-B pathway, which is particularly crucial to anti-tumor immunity[88]. Not just innate immune cells but even adaptive immunity cells can be significantly impacted by STAT3. Notably, STAT3 can affect myeloid-derived suppressor cells (MDSCs), newly discovered immature myeloid cells having the capacity to inhibit immune responses and grow during cancer and inflammatory disorders[89]. In order to promote MDSCs' detrimental effect on immune cells, STAT3 may, for example, directly boost the expression of indoleamine 2,3-dioxygenase (IDO) and interfere with the production of interferon regulatory factor-8[90]. Recent studies on CAFs shown that overexpression of STAT3 stimulated the production of immunosuppressive factors, which resulted in the oncogenic phenotype[91, 92]. As a result, the newest preclinical research is seeing great success with STAT3 inhibitors paired with immunotherapy, particularly when combination with immune-checkpoint inhibitors and chimeric antigen receptor T cells. Bevacizumab, a monoclonal antibody that targets VEGF, and atezolizumab, a PD-L1 inhibitor, have recently been shown to work well together to extend the overall survival and progression-free survival of patients with unresectable HCC in phase III clinical trials[93]. Furthermore, it has been demonstrated that STAT3 regulates CAR-T cell treatment, a novel and successful immunotherapy

[94]. The combination of STAT3 inhibitors with cancer immunotherapy has considerable potential in each of these situations.

5. Conclusion

Through years of research and development, cancer immunotherapy has been able to control and modify immune responses in cancer patients. Recently, cancer treatments have tended to use the immune system to target and destroy tumor cells precisely rather than just targeting tumor cells broadly. Cancer immunotherapy, however, still has its own drawbacks in comparison to standard cancer treatment. First and foremost, whether cancer tissue is "immune suppression type" or "immune exclusion type," the response to cancer immunotherapy is generally fairly low. The limitations of each subtype of cancer immunotherapy are varied. The expression of the targeted molecule on tumor cells places restrictions on mAb treatment. Cytokines have less steady therapeutic effectiveness and may cause unmanageable toxicity inside of patients' bodies. As for ICIs, they are unable to have a safe curative influence on children. Cancer vaccinations cannot protect those with compromised immune systems. Therefore, the key to developing an effective cancer therapy is the discovery of multiple levels of tumor immune therapy, including immune cell activation, immune cell infiltration, and neoantigen detection. It has been proven that the current inadequacy of a single cancer immune treatment can be made up for by the combination of signaling pathway inhibitors. In the future, more cancer patients will likely benefit from immuno-oncology research, both being conducted and yet to be found.

6. Figure Legend:

Figure 1: This picture presents a brief history of cancer immunotherapy. Every significant event happened in each year of history was listed in the figure.

Figure 2: This picture represents the place where checkpoint molecule pairs exist. It also presented their three different locations, including T lymphocytes, an antigen-presenting cell (APC) and tumor cells.

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