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ADVANCES IN IMMUNO-ONCOLOGY: PROSPECTS, CHALLENGES AND EMERGING TRENDS

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ABSTRACT

Nowadays, cancer immunotherapy is a cutting-edge malignancy treatment. Immunotherapy has been shown to offer unmatched benefits over conventional anti-tumor therapy in several experimental and clinical studies, which can increase both progression-free survival (PFS) and overall survival (OS). On the other hand, immunotherapy is unclear and complex. A hyperactive immune system might potentially result in serious side effects from immunotherapy. Immunological checkpoints that are more efficient and have fewer side effects are constantly being investigated. By weighing the benefits and drawbacks of immunotherapy and closely monitoring its future development trend, this review provides an overview of current advancements in the field. It suggests a new approach to tumor treatment. In terms of survival rates and overall quality of life, cancer immunotherapy has led to substantial advancements in patient outcomes compared to traditional treatments like chemotherapy, radiation, and surgery. It has become a key component of modern cancer care, with applications ranging from early-stage (adjuvant and neo adjuvant) settings to advanced metastatic disease across various cancer types.

Keywords: Cancer immunotherapy, Immune checkpoint blockade therapies, natural killer (NK) cells, ACI (adoptive cellular Immunotherapy) TGR (tumor growth rate)

1. INTRODUCTION:

Immuno-oncology has profoundly transformed the landscape of cancer treatment. The origins of this approach can be traced back to the late 19th century with the work of William B. Coley, often referred to as the pioneer of cancer immunotherapy. While treating patients with bone sarcomas, Coley noticed that some individuals who developed severe infections after surgery common at the time due to limited aseptic methods experienced unexpected tumor shrinkage **[1]**. Motivated by these observations, he began experimenting in 1891 by injecting a mixture of live and inactivated bacteria, notably *Streptococcus pyogenes* and *Serratia marcescens*, into cancer patients. His goal was to provoke an immune response capable of attacking tumors. This bacterial mixture, later known as "Coley's toxin," is considered the earliest recorded example of an active immunotherapy used against cancer **[2]**.

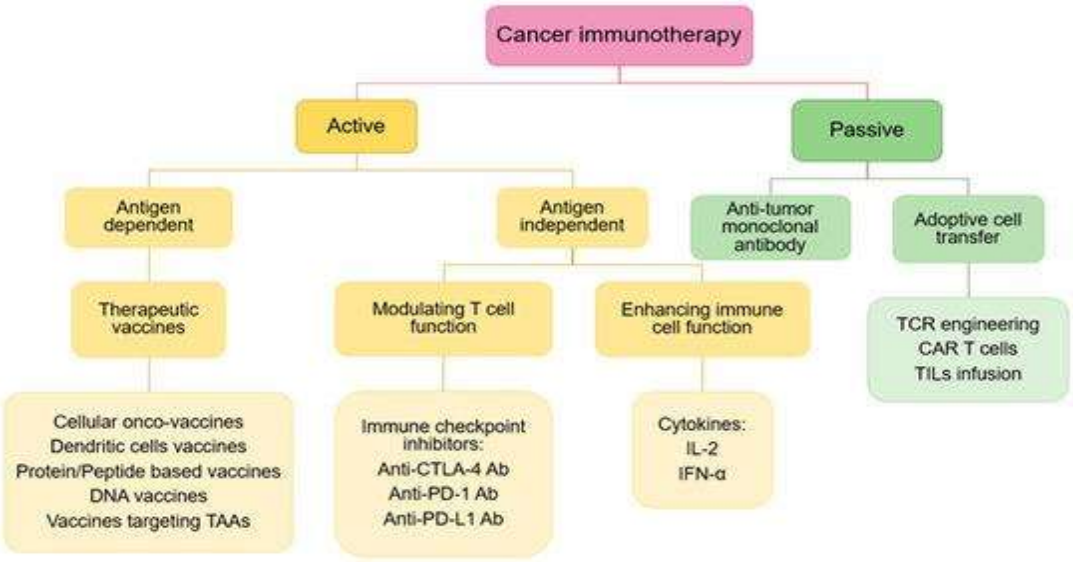

Figure 1: Schematic classification of immunotherapies designed for cancer

Immunotherapy represents an advanced form of cancer treatment that actively harnesses and regulates the immune system to identify and destroy cancer cells across various targets and pathways. Unlike traditional methods such as chemotherapy and radiation, which directly attack tumors, immunotherapy focuses on enhancing the body's natural defenses by modifying the tumor microenvironment, thereby empowering immune cells to recognize and eliminate cancer at multiple crucial points **[3]**.

2. TUMOR CELL IMMUNOTHERAPY

Immune cells have the ability to detect and destroy tumor cells. By activating these cells and leveraging the body's own tumor-specific immune mechanisms, it is possible

to restore their role in monitoring and eliminating cancer, even in cases where tumors have evaded immune detection. While cellular immunotherapy has shown promising results in the treatment of blood-related cancers, its success in targeting solid tumors has been limited due to the complexity and diversity of these tumors, as well as challenges posed by their surrounding microenvironment **[4]**.

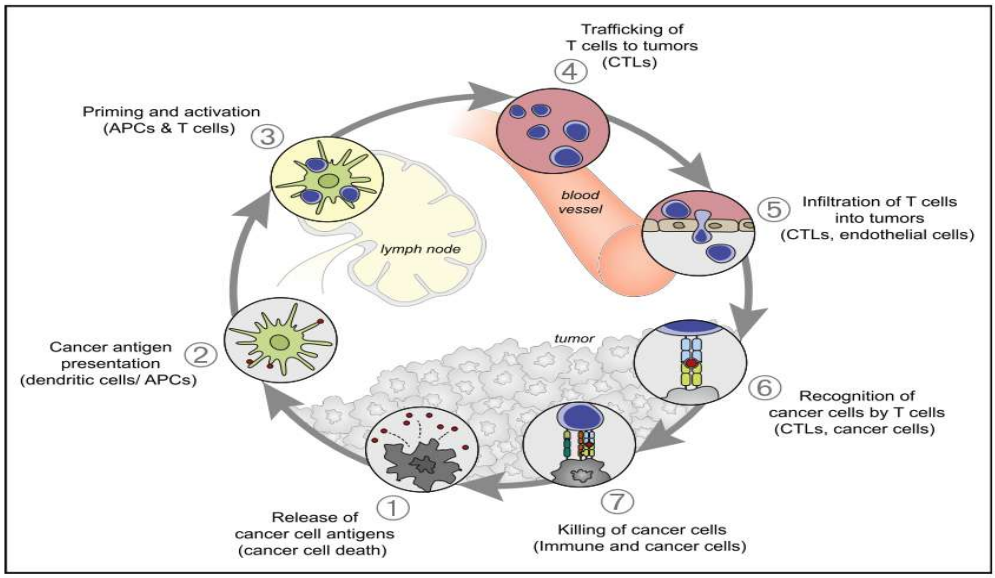

Figure 2: Schematic diagram of the cancer immune cycle

2.1 Cell-based immunotherapy (ACI)

Adoptive transfer of immune cells (ACI) involves the elimination of cancer cells through the infusion of immune effector cells that have been genetically modified and expanded outside the body. This approach has gained considerable attention in cancer research due to its high specificity, ability to be preserved effectively, and minimal risk of drug resistance. ACI is generally divided into two types: specific and non-specific. In non-specific ACI, immune cells are activated by lymphocytes or cytokines from peripheral blood, enabling them to attack various types of tumors. However, because of their limited tumor-targeting ability and relatively weak cytotoxicity, they are primarily applied as supportive treatments rather than standalone therapies.

Examples of immune effector cells involved in nonspecific adoptive cellular immunotherapy (ACI) include tumor-infiltrating lymphocytes (TIL), natural killer cells (NKCs), cytokine-induced killer cells (CIKs), dendritic cells (DCs), lymphocyte-activated killer cells (LAKs), and macrophage-activated killer cells (MAKs), among others. In contrast, specific ACI activates immune cells through targeted tumor antigens and specialized stimulatory agents, such as TIL therapy, T cell receptor-

engineered T cells (TCR-T), and chimeric antigen receptor T-cell (CAR-T) immunotherapy. This targeted approach is valued for its potent antitumor effects, precise targeting, high specificity, limited side effects, and resistance to drug resistance, making it suitable for advanced cancer patients or those unresponsive to other treatments. However, due to the difficulties in isolating and expanding TILs, this therapy is currently mainly limited to melanoma, while CAR-T therapy is predominantly applied in the treatment of hematologic malignancies **[5]**.

2.2 Therapy using natural killer cells.

Natural killer (NK) cells, a type of potent innate immune cell, predominantly express killer activation receptors (KARs) and killer inhibitory receptors (KIRs) on their surface. These cells can directly destroy target cells and trigger a comprehensive immune response without relying on antibodies. NK cells are especially effective against hematologic and metastatic cancers by targeting tumor cells that either exhibit increased levels of activating ligands or lack MHC class I molecules **[6]**.

Additionally, natural killer (NK) cells can recognize and destroy tumor cells that are marked by antibodies through antibody-dependent cell-mediated cytotoxicity (ADCC), while cytokines such as IL-2 and IL-5 play a crucial role in promoting and sustaining NK cell activation **[7]**. Nonetheless, neoplastic cells still possess the ability to suppress NK cells to accomplish immunological escape. Initially, tumor cells release MICA and MICB proteins, leading to the development of targeted antibodies like antibody clone 7C6 that demonstrate specific therapeutic effects. Additionally, tumor cells evade natural killer cell (NKC) attack by up regulating HLA-G, which binds to the inhibitory receptor LIR on NK cells, thereby blocking their activity. Moreover, the anti-cancer functions of NK cells can be hindered either directly or through cytokine secretion by suppressive immune cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) **[8]**.

NK cell activation is mediated by the following mechanisms:

1) Reducing the interaction between MHC-I molecules and the inhibitory receptor KIR
2) Enhancing the binding affinity to activated antigens.
3) ICIs were used to eliminate immunosuppressive signals.
4) The identification and destruction of tumor cells is mediated by ADCC.
5) Cytokines encourage NK cell activation.

The following are the processes by which NK cells are inhibited:

1) Tumor cells increase the binding to inhibitory receptor LIR1 and up regulate the production of HLA-G.

2) The interaction between NKG2D ligands on tumor cells and the NKG2D receptor on NK cells leads to a reduction in antibody-mediated immune activity.
3) Tumor cells release MICA and MICB proteins as a mechanism to evade cell death.
4) To prevent the lethal effect, MDSC and Tregs release cytokines.

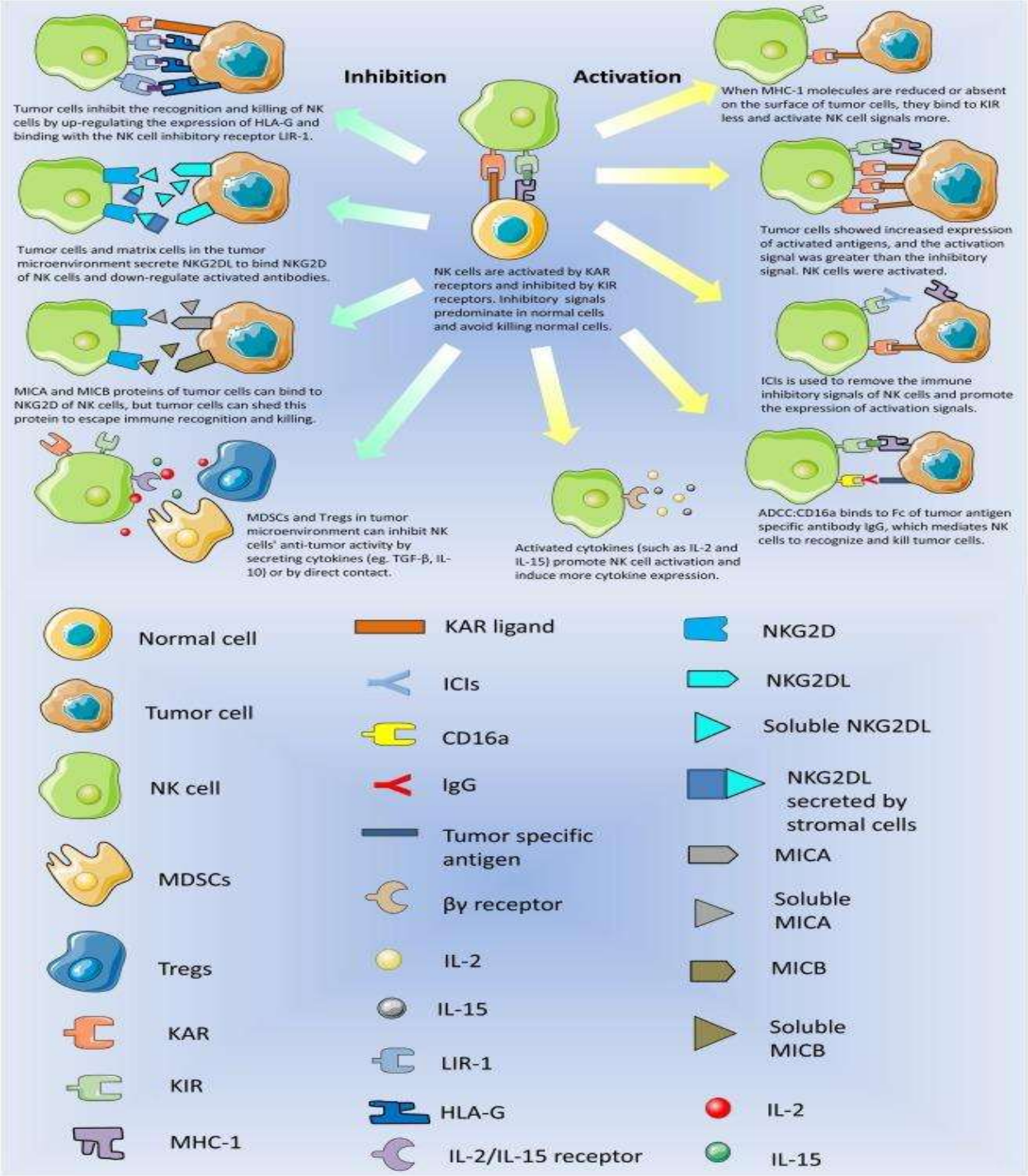

Figure 3: NK cell activation and inhibition methods. KAR and KIR are components of NK cells. The way that NK cells react to tumor cells is determined by their activation and inhibition signals

2.3. Immunotherapy using T-cells engineered with chimeric antigen receptors (CAR-T cells)

CAR-T refers to chimeric antigen receptor T-cell immunotherapy, a potent form of adoptive cell therapy. This approach involves extracting the patient's T cells through leukocyte reduction, genetically modifying them to express CARs on their surface, and then reintroducing them to specifically target and eliminate tumor cells. This therapy has demonstrated a high rate of remission in cancers that display CD19 proteins, such as large B-cell lymphoma and B-cell acute lymphoblastic leukemia. Currently, the FDA has approved treatments like axicabtagene ciloleucel (YesCarta) from Kite/Gilead and tisagenlecleucel-T (Kymriah) from Novartis. Kymriah is specifically utilized for managing relapsed or treatment-resistant B-cell acute lymphoblastic leukemia **[9]**.

Despite potential side effects such as cytokine release syndrome (CRS) and neurotoxicity, Yescarta has proven effective in managing relapsed or refractory large B-cell lymphoma in adults. Research on T-cell depletion has also progressed considerably, with key objectives including effective cancer treatment, minimizing T-cell loss, and expanding patient access to the therapy **[10]**.

a. A deficiency in the TET2 protein can enhance T cell muscle memory, prolong their presence in the central memory phase, reduce the likelihood of target cell resistance, boost the production of granzyme and perforin enzymes, and improve the overall effectiveness of CAR-T therapy. Additionally, modifying the TET2 protein or gene through pharmaceuticals or gene-editing techniques may help lower post-treatment production costs **[11]**.

b. The absence of Nr4a transcription factors has been shown to significantly enhance the performance of CAR-T cells. These factors are typically overexpressed in CD8+ T cells during chronic viral infections and in cancer. In animal studies, mice with CAR-T cells lacking Nr4a exhibited reduced tumor size and extended survival. Targeting Nr4a expression is expected to become a promising strategy for combating T-cell exhaustion in future therapies **[12]**.

3. ICIS [IMMUNE CHECKPOINT INHIBITORS]

The immune checkpoint, located on the surface of T cells or tumor cells, functions to regulate T cell over-activation. Normally, this inhibitory checkpoint protein protects against autoimmune damage; however, when interacting with tumor cells, it blocks T cells from approaching the tumor,

hindering the immune system's ability to recognize and destroy cancerous cells **[13]**. Immune checkpoint inhibitors (ICIs) can greatly enhance T cell activity and revive the immune system's ability to fight tumors.

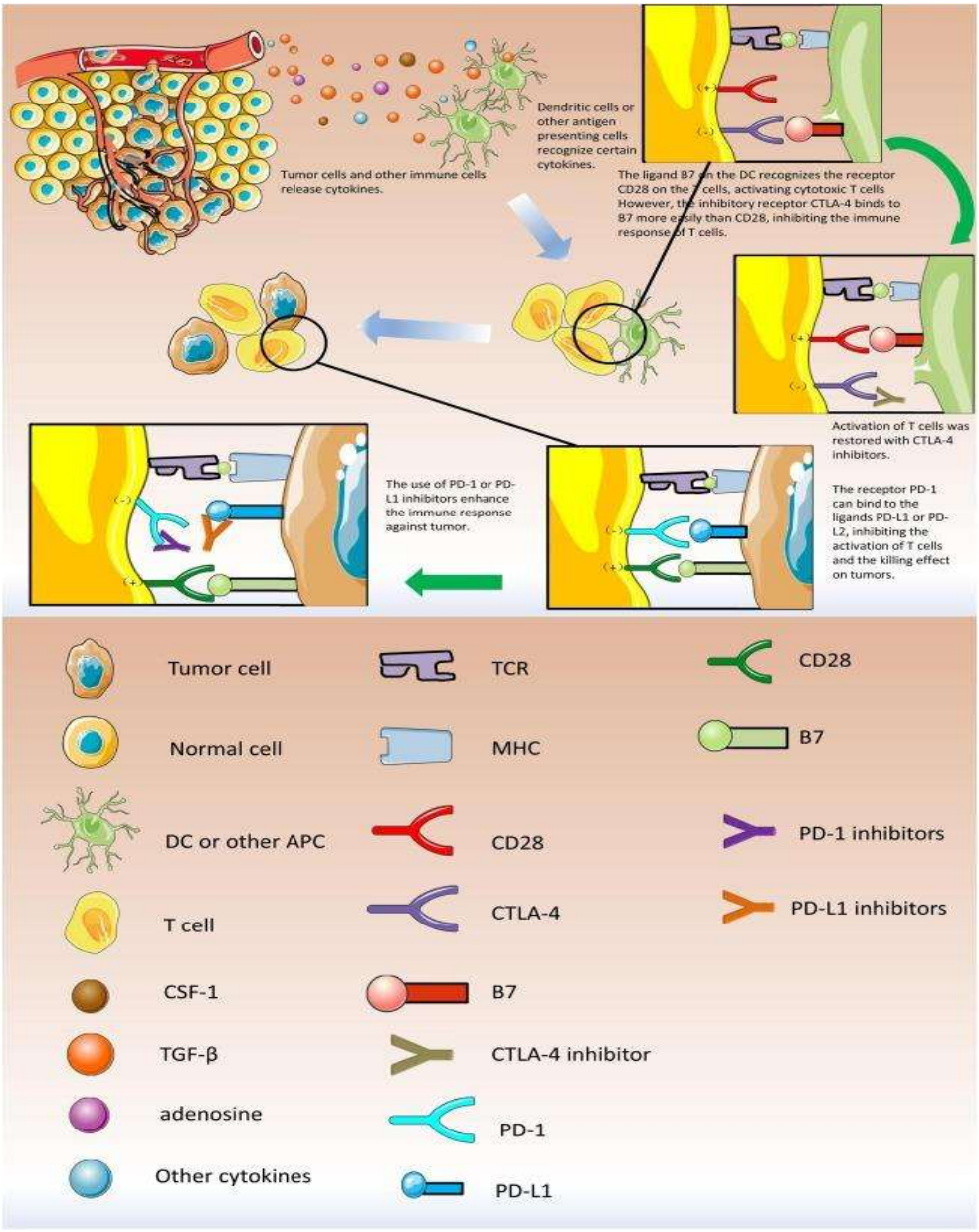

Figure 4: Immune checkpoint inhibitors (ICIs) enhance the body's cancer-fighting capabilities

Within the tumor microenvironment, tumor cells and various immune cells release cytokines like adenosine, TGF-β, and CSF-1, which are detected by dendritic cells (DCs) and other antigen-presenting cells. The ligand B7 on DCs interacts with the CD28 receptor on T cells, activating cytotoxic T cells and promoting their migration and expansion toward tumor sites. In activated T cells, the inhibitory receptor CTLA-4 has a higher affinity for B7 than CD28, which suppresses the immune

response by preventing T cell activation. To counter this, CTLA-4 inhibitors are employed to reactivate T cells. Activated T lymphocytes then target tumor cells. Additionally, the PD-1 receptor on T cells can bind to PD-L1 or PD-L2 ligands on tumor cells, blocking T cell activation and their ability to kill tumors. Treatment with PD-1 or PD-L1 inhibitors in living organisms has been shown to enhance T cell responses against cancers, inhibit tumor progression, and improve patient survival rates.

3.1 Improve the effectiveness of immune checkpoint inhibitors (ICIs).

In clinical settings, PD-1/PD-L1 inhibitors have demonstrated approximately 80% effectiveness in treating lymphoma and around 60% in cancers characterized by high microsatellite instability (MSI-H). However, their response rates in other frequently occurring solid tumors range between 10% and 30% **[14]**. Immune system-targeted treatment is expensive, though, and if it doesn't work, it might postpone the illness. Therefore, a major objective in immunotherapy research is to improve the efficacy of immune checkpoint inhibitors (ICIs) to achieve targeted and personalized cancer treatment.

a. Finding prognostic biomarkers and therapeutic responsiveness

CyTOF technology can distinguish various cell types in a patient's blood prior to administering PD-1/PD-L1 inhibitor therapy. Although the ratio of monocytes within peripheral blood mononuclear cells is generally considered a baseline predictor of patient response, the most reliable marker for forecasting both progression-free and overall survival is the count of $CD14^{+}CD16^{+}$HLA-DR^hi monocytes **[15]**.

b. A mix of at least two ICIs.

Targeting specific immune checkpoints such as increased PD-1 expression on tumor cells and the activation of $PD\text{-}L1^{+}$/$VISTA^{+}$ T cells and $CD68^{+}$ macrophages after treatment with CTLA-4 inhibitors alone—can help preserve the antitumor activity of alternative inhibitory pathways. Anti-PD-1 therapy mainly acts within the tumor microenvironment to prevent T cell exhaustion during the effector phase, while anti-CTLA-4 therapy supports the initial activation of T cells within lymphoid tissues **[16]**.

c. Developing a model to forecast ICI effectiveness [17]

According to clinical experience, several factors, such as Tumor-host interactions are shaped by a variety of factors, including the genetic makeup of the host, the genomic profile of the tumor, the expression levels of PD-1 and PD-L1, the surrounding tumor microenvironment, and the gut micro biome composition which determine an inhibitor's effectiveness. Predictive models should be

updated and evaluated frequently for the benefit of patients.

d. Transforming inflammatory cells from Tregs [18]

By suppressing effector T cells during the tumor development process, Tregs encourage tumor growth; this also affects the success rate of cancer immunotherapy **[19]**. The present research indicates that blocking the CARMA1-BCL10-MALT1 (CBM) signalosome can transform inhibitory Tregs into inflammatory cells that produce IFNγ. This shift triggers an inflammatory reaction within the tumor, halting its progression and enhancing the tumor cells responsive to immunotherapy. Combining Mepazine, which inhibits MALT1, with anti-PD-1 immune checkpoint inhibitors significantly, slows down tumor growth.

3.2. Common ICI classification

T-cells activated by antigens express PD-1 receptors on their surface, which interact with both tumor cells and other T-cells. When these receptors bind to the ligands PD-L1 and PD-L2, they suppress T-cell activation. Blocking the PD-1/PD-L1 pathway not only boosts the immune response of T-cells against tumors but also influences tumor-associated macrophages (TAMs) by restoring their ability to engulf cancer cells, thereby slowing tumor progression and improving patient outcomes.

PD-1/PD-L1 inhibitors are generally safer; more targeted, and cause fewer side effects than CTLA-4 inhibitors. These monoclonal antibodies have been widely applied in treating various cancers, including melanoma, non-small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, urothelial carcinoma, gastric cancer, renal cancer, liver cancer, and several other malignancies **[20]**.

The following medications are examples of antagonists that target the PD-1 receptor targeting involve the use of monoclonal antibodies against PD-1 and PD-L1 **[21]**:

a. Pembrolizumab (Keytruda) showed in the KEYNOTE trials that it significantly prolonged survival in patients with locally advanced or metastatic non-small cell lung cancer compared to platinum-based chemotherapy. It also achieved a higher response rate in these cancers and enhanced both overall survival (OS) and progression-free survival (PFS) in individuals with solid tumors.

b. The combination of Tecentriq (Atezolizumab) and chemotherapy prolonged progression-free survival, greatly improved treatment effectiveness, and resulted in a 17% increase in the rate of tumor shrinkage.

c. Nivolumab, or Opdivo, has demonstrated greater effectiveness in treating cancers of the oral cavity and upper respiratory tract, as well as gastric malignancies. In a clinical

study, 12% of patients responded to Opdivo therapy regardless of their levels of PD-L1 expression.

Research into Siglec-15, a newly identified target, is advancing rapidly. Siglec-15 suppresses T cell activity, thereby weakening the immune system's ability to fight tumors and enabling cancer cells to evade immune detection. Elevated expression of Siglec-15 has been observed in various cancers, such as those affecting the bladder, kidney, liver, and lungs **[22]**.

4. ELEMENTS THAT AFFECT TUMOR IMMUNOTHERAPY

Human immunity, closely connected to the body's internal micro biome and genetic makeup **[23]**, plays a crucial role. Additionally, tumor characteristics are important: factors such as the quantity of new antigens derived from clones, mutation targets within tumor cells, tumor mutation burden, and the diversity of tumor neoantigens within the tumor significantly influence treatment outcomes. Patients exhibiting a high count of clonal neoantigens alongside low variability of tumor neoantigens tend to experience better therapeutic responses **[24]**. Furthermore, environmental factors like daily routine.

4.1. Tumor type's impact on effectiveness

Based on the tumor's immune characteristics, it can be classified into three types: the first is called "immuno suppressed," or "immune desert type," and its central and peripheral regions either lack T cells or, if they do, have a low cell density and number. This kind of immune suppression is primarily caused by tumor-specific killer T cells. In clinical settings, PD-1/PD-L1 treatment is essentially ineffectual for this kind.

The second tumor type, known as the "immune excluded" or immune evasion category, features abundant CD3+ and CD8+ lymphocytes at the tumor's periphery. However, these immune cells fail to penetrate the tumor's interior. The main reason for the weakened immune response is the ability of T cells to evade infiltration.

The third category, called the "immunologically inflamed" type, is characterized by the presence of pro-inflammatory molecules and immune cells such as PD-L1 around the tumor. Despite this, the tumor manages to suppress the immune attack by escaping detection or neutralizing the immune response **[25]**.

4.2. How the tumor microenvironment influences treatment outcomes

The tumor microenvironment consists of cancer cells, fibroblasts, blood vessel lining cells, newly formed blood vessels, surrounding immune cells, and the extracellular matrix **[26]**. In clinical practice, the degree of tumor degeneration, the likelihood of immunotherapy medications working, and other factors can be ascertained by assessing the immune cell

composition, quantity, and other characteristics in the tumor center and surrounding microenvironment.

Meanwhile, by integrating environmental and genetic factors, it is possible to anticipate the immunotherapy of inflammatory tumors. Potential drug targets encompass inflammatory cells, signaling molecules involved in inflammation, and crucial proteins within inflammatory pathways. Additionally, the acidic and low-oxygen conditions within the tumor microenvironment encourage tumor progression and proliferation, hinder T-cell activation and function, and greatly weaken the body's immune defense against the tumor **[27]**.

4.3. Neoantigens

The main causes of anti-PD1/CTLA4 immunotherapy's declining effectiveness are the intratumoral heterogeneity (ITH) of neo antigens, a shortage of clonal neoantigens combined with an increase in subclonal neoantigens impacts patient outcomes. When tumors produce a higher number of clonal neoantigens and exhibit lower heterogeneity, patients tend to experience longer overall survival. In tumors rich in neoantigens, elevated levels of clonal neoantigens correlate with increased expression of pro-inflammatory genes such as PD-L1, IL-6, and IFN-γ. Consequently, immunotherapy tends to be more effective when clonal neo antigen levels are high and intra-tumor heterogeneity is low. However, extensive radiotherapy across multiple sites may lead to the emergence of numerous subclonal neoantigens, reducing the proportion of clonal neoantigens and potentially diminishing the success of immunotherapy **[28]**. As a result, even though these patients have a large number of mutations overall, immunotherapy is not very effective. The precise mechanism is still being researched and debated.

5. DISCUSSION

5.1. The immunotherapy medication resistance mechanism

Cancer immunity involves processes of immune surveillance, equilibrium, and evasion. Tumor cells evade detection and destruction by the immune system through strategies such as attracting immune regulatory cells, reducing the expression of tumor antigens, and releasing immune-suppressive factors. These mechanisms allow tumors to spread and develop into detectable masses. Additionally, the selective enhancement of immune-evasive proteins like PD-L1, arachidonic acid lipoxygenase, and IDO1/IDO2 can further support tumor progression **[29]**.

5.2. Primary immunological resistance mechanisms

Tumor-specific T cells exert anticancer effects by producing interferon-γ, which helps antigen-presenting cells (APCs)

recognize tumor cells and their related antibodies. This process not only attracts more immune cells but also directly inhibits tumor growth, encourages tumor cell apoptosis, enhances the presentation of tumor antigens, and boosts the levels of proteins involved in antigen presentation, such as the major histocompatibility complex (MHC) molecule **[30]**.

5.3. How acquired immunological resistance works

During an anti-tumor immune response, lymphocytes that have entered the tumor environment can release significant amounts of interferon-gamma (IFN-γ), which in turn triggers tumor cells to express PD-L1. When combined with CTL PD1, PD-L1 can prevent effector T cells' immune-killing effects on tumors **[31]**.

5.4. Tumor resistance treatment strategies

Although it is challenging to prevent tumor cell resistance during tumor treatment, patients can receive the best possible outcomes by using the right strategies. Before starting treatment, the right population should receive immunotherapy. To determine a patient's suitability for therapy, evaluations may include analysis of gut micro biota, assessment of tumor biomarkers, and detection of mutations in the PBRM1 gene. To increase the tumor cells' susceptibility to immunotherapy, hasten their destruction, and prevent the development of drug resistance in tumor cells, patients are then given customized treatment plans and combination therapies **[32]**.

6. CONCLUSIONS AND OUTLOOKS FOR THE FUTURE

Anti-tumor immunotherapy is becoming more and more significant in the field of tumor therapy these days. Treatment trials for a variety of malignant cancers have shown encouraging results. By identifying new targets and innovative techniques like combination therapy, immunotherapy's effectiveness is

increased and bad responses are decreased. Immunotherapy is still controversial, though, for several reasons, including blindness, empirical limitations, and severe side responses, potentially severe outcomes, uncertain treatment responses and significant financial costs are major concerns **[33]**.

Table 1 lists all of immunotherapy's benefits and drawbacks. To achieve the best possible therapeutic outcome and help tumor patients regain their health, A comprehensive understanding of the dynamic and intricate nature of tumor development is essential for crafting a personalized immunotherapy strategy. This approach should be tailored to the patient’s specific immune profile and the unique features of their tumor, allowing for more precise and effective treatment. As a

cutting-edge approach in cancer care, immunotherapy offers substantial progress beyond traditional methods, holding great promise for improving outcomes in advanced-stage cancer.

This can be achieved by following three key strategies: identifying novel targets involved in core functional pathways, focusing immune suppression specifically within the tumor microenvironment and recognizing the tumor itself as the source of this immunosuppressive environment are also essential components. Immunotherapy is a field that will develop and encounter many chances and obstacles.

Table 1: The benefits and drawbacks of immunotherapy

Benefits of Immunotherapy	Drawbacks of immunotherapy
1. "Immuno inflammatory" tumors respond well to treatment, and the extended lifespan has increased considerably.	**1. The treatment objects have restrictions, and the users have high selectivity. Immunotherapy has a poor effect on tumors of the "immune suppression type" and "immune exclusion type."**
2. Immunotherapy offers precise targeting with exceptional selectivity and effectiveness in recognizing and attacking cancer cells.	**2. Immune Checkpoint inhibitor use may result in negative regulation, which may cause autoimmune disorders or even death.**
3. The benefits of Immune-based treatment endure effectively for a long time.	**3. After use, some patients may experience a range of non-specific hazardous and side effects, including hyperprogressive disease, which could hasten their demise.**
4. Broad flexibility. Numerous tumor types can be controlled and eliminated by the treatment.	**4. Numerous factors influence immunotherapy's effectiveness. Patients' prognosis and survival rate are unknown.**
5. Have perseverance. Long-term tumor cell death and immune function restoration are achieved by the treatment, which activates the body's immune system.	**5. The expense of treatment is high.**
6. Be thorough. It can completely detect, locate, and eliminate tumor cells, strengthen and repair the body's immune system, and successfully stop tumor spread.	

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REFERENCES

[1] McCarthy EF. The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. Iowa Orthop J. 2006; 26: 154–8.

[2] J. Couzin-Frankel, Breakthrough of the year 2013. Cancer immunotherapy, Science 342 (6165) (2013) 1432–1433.

[3] H. Ikeda, H. Shiku, Immunotherapy of solid tumor: perspectives on vaccine and cell therapy, Nihon Rinsho 70 (12) (2012) 2043–2050.

[4] H.E. Marei, A. Althani, T. Caceci, R. Arriga, T. Sconocchia, A. Ottaviani, G. Lanzilli, M. Roselli, S. Caratelli, C. Cenciarelli, G. Sconocchia, Recent perspective on CAR and Fc Gamma-CR T cell immunotherapy for cancers: preclinical evidence

versus clinical outcomes, Biochem. Pharmacol. 166 (2019) 335–346.

[5] A. Panda, A. Betigeri, K. Subramanian, J.S. Ross, D.C. Pavlick, S. Ali, P. Markowski, A. Silk, H.L. Kaufman, E. Lattime, J.M. Mehnert, R. Sullivan, C.M. Lovely, J. Sosman, D.B. Johnson, G. Bhanot, S. Ganesan, Identifying a Clinically Applicable Mutational Burden Threshold as a Potential Biomarker of Response to Immune Checkpoint Therapy in Solid Tumors, JCO Precis Oncol 2017 (2017).

[6] M. Shevtsov, G. Multhoff, Immunological and translational aspects of NK cell-based antitumor immunotherapies, Front. Immunol.

[7] C. Cantoni, L. Huergo-Zapico, M. Parodi, M. Pedrazzi, M.C. Mingari, A. Moretta, B. Sparatore, S. Gonzalez, D. Olive, C. Bottino, R. Castriconi, M. Vitale, N.K. Cells, Tumor Cell Transition, and Tumor Progression in Solid Malignancies: New Hints for NK-Based Immunotherapy? J. Immunol. Res. 2016 (2016) 4684268.

[8] L. Ferrari de Andrade, R.E. Tay, D. Pan, A.M. Luoma, Y. Ito, S. Badrinath, D. Tsoucas, B. Franz, K.F. May Jr., C.J. Harvey, S. Kobold, J.W. Pyrdol, C. Yoon, G.C. Yuan, F.S. Hodi, G. Dranoff, K.W. Wucherpfennig, Antibody-mediated inhibition of MICA and MICB shedding promotes NK cell-driven tumor immunity, Science 359 (6383) (2018) 1537–1542.

[9] M.G. Morvan, L.L. Lanier, NK cells and cancer: you can teach innate cells new tricks, Nat. Rev. Cancer 16 (1) (2016) 7–19.

[10] F. Kroschinsky, F. Stolzel, S. von Bonin, G. Beutel, M. Kochanek, M. Kiehl, P. Schellongowski, H. Intensive Care in, G. Oncological Patients Collaborative, New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management, Crit Care 21 (1) (2017) 89.

[11] E.J. Wherry, M. Kurachi, Molecular and cellular insights into T cell exhaustion, Nat. Rev. Immunol. 15 (8) (2015) 486–499.

[12] J. Chen, I.F. Lopez-Moyado, H. Seo, C.J. Lio, L.J. Hempleman, T. Sekiya, A. Yoshimura, J.P. Scott-Browne, A. Rao, NR4A transcription factors limit CAR T cell function in solid tumours, Nature 567 (7749) (2019) 530–534.

[13] A.L. Xia, J.C. Wang, K. Yang, D. Ji, Z.M. Huang, Y. Xu, Genomic and epigenomic perspectives of T-cell exhaustion in cancer, Brief.

Funct. Genomics 18 (2) (2019) 113–118.

[14] A.G. Ramsay, Immune checkpoint blockade immunotherapy to activate antitumor T-cell immunity, Br. J. Haematol. 162 (3) (2013) 313–325.

[15] Y. Yu, Molecular classification and precision therapy of cancer: immune checkpoint inhibitors, Front. Med. 12 (2) (2018) 229–235.

[16] C. Krieg, M. Nowicka, S. Guglietta, S. Schindler, F.J. Hartmann, L.M. Weber,R. Dummer, M.D. Robinson, M.P. Levesque, B. Becher, High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy, Nat. Med. 24 (2) (2018) 144–153.

[17] D.T. Proctor, Z. Patel, S. Lama, L. Resch, G. van Marle, G.R. Sutherland, Identification of PD-L2, B7-H3 and CTLA-4 immune checkpoint proteins in genetic subtypes of meningioma, Oncoimmunology 8 (1) (2019) e1512943..

[18] J.J. Havel, D. Chowell, T.A. Chan, The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy, Nat. Rev. Cancer 19 (3) (2019) 133–150.

[19] M. Di Pilato, E.Y. Kim, B.L. Cadilha, J.N. Prussmann, M.N. Nasrallah, D. Seruggia, S.M. Usmani, S. Misale, V. Zappulli, E. Carrizosa, V. Mani, M. Ligorio, R.D. Warner, B.D. Medoff, F. Marangoni, A.C. Villani, T.R. Mempel, Targeting the CBM complex causes Treg cells to prime tumours for immune checkpoint therapy, Nature 570 (7759) (2019) 112–116.

[20] P.A. Savage, D.S. Leventhal, S. Malchow, Shaping the repertoire of tumor-infiltrating effector and regulatory T cells, Immunol. Rev. 259 (1) (2014) 245–258.

[21] H.K. Angell, J. Lee, K.M. Kim, K. Kim, S.T. Kim, S.H. Park, W.K. Kang, A. Sharpe,J. Ogden, A. Davenport, D.R. Hodgson, J.C. Barrett, E. Kilgour, PD-L1 and immune infiltrates are differentially expressed in distinct subgroups of gastric cancer, Oncoimmunology 8 (2) (2019) e1544442.

[22] B. Bian, D. Fanale, N. Dusetti, J. Roque, S. Pastor, A.S. Chretien, L. Incorvaia, A. Russo, D. Olive, J. Iovanna, Prognostic significance of circulating PD-1, PD-L1, pan-BTN3As, BTN3A1 and BTLA in patients with pancreatic

adenocarcinoma, Oncoimmunology 8 (4) (2019) e1561120.

[23] J. Wang, J. Sun, L.N. Liu, D.B. Flies, X. Nie, M. Toki, J. Zhang, C. Song, M. Zarr, X. Zhou, X. Han, K.A. Archer, T. O'Neill, R.S. Herbst, A.N. Boto, M.F. Sanmamed, S. Langermann, D.L. Rimm, L. Chen, Siglec-15 as an immune suppressor and potential target for normalization cancer immunotherapy, Nat. Med. 25 (4) (2019)656–666.

[24] J. Tang, Z. Xu, L. Huang, H. Luo, X. Zhu, Transcriptional regulation in model organisms: recent progress and clinical implications, Open Biol. 9 (11) (2019)190183.

[25] N. McGranahan, A.J. Furness, R. Rosenthal, S. Ramskov, R. Lyngaa, S.K. Saini, M. Jamal-Hanjani, G.A. Wilson, N.J. Birkbak, C.T. Hiley, T.B. Watkins, S. Shafi,N. Murugaesu, R. Mitter, A.U. Akarca, J. Linares, T. Marafioti, J.Y. Henry, E.M. Van Allen, D. Miao, B. Schilling, D. Schadendorf, L.A. Garraway, V. Makarov, N.A. Rizvi, T. Riegger, S. Conrad, H.J. Schluesener, H.P. Kaps, A. Badke, C. Baron, J. Gerstein,K. Dietz, M. Abdizahdeh, J.M. Schwab, Immune depression syndrome following human spinal cord injury (SCI): a pilot study, Neuroscience 158 (3) (2009) 1194–1199.

[26] X. Zhu, H. Luo, Y. Xu, Transcriptome analysis reveals an important candidate gene involved in both nodal metastasis and prognosis in lung adenocarcinoma, Cell Biosci. 9 (1) (2019).

[27] Y. Sun, R. Wang, M. Qiao, Y. Xu, W. Guan, L. Wang, Cancer associated fibroblasts tailored tumor microenvironment of therapy resistance in gastrointestinal cancers, J. Cell. Physiol. 233 (9) (2018) 6359–6369.

[28] J. Liu, D. Li, H. Luo, X. Zhu, Circular RNAs: The star molecules in cancer, Mol. Aspects Med. 70 (2019) 141–152.

[29] M.S. Rooney, S.A. Shukla, C.J. Wu, G. Getz, N. Hacohen, Molecular and genetic properties of tumors associated with local immune cytolytic activity, Cell 160 (1-2) (2015) 48–61.

[30] J. Gao, L.Z. Shi, H. Zhao, J. Chen, L. Xiong, Q. He, T. Chen, J. Roszik, C. Bernatchez, S.E. Woodman, P.L. Chen, P. Hwu, J.P. Allison, A. Futreal, J.A. Wargo, P. Sharma,Loss of IFN-gamma

pathway genes in tumor cells as a mechanism of resistance to Anti-CTLA-4 therapy, Cell 167 (2) (2016) 397–404 e9.

[31] C. Liu, A.C. Gao, IFNgamma, a Double-Edged Sword in Cancer Immunity and Metastasis, Cancer Res. 79 (6) (2019) 1032–1033.

[32] L. Schultz, R. Gardner, Mechanisms of and approaches to overcoming resistance to immunotherapy, Hematology Am. Soc. Hematol. Educ. Program 2019 (1) (2019) 226–232.

[33] M.F. Sanmamed, L. Chen, A Paradigm Shift in Cancer Immunotherapy: From Enhancement to Normalization, Cell 176 (3) (2019) 677.