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The Mechanisms of Immune Evasion in Cancer Stem Cells and Related Immunotherapy Advances

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Abstract: Cancer Stem Cells (CSCs), as a unique subset of tumor cells, play a crucial role in tumor initiation, progression, and recurrence due to their self-renewal and differentiation capabilities. CSCs exhibit significant immune evasion abilities, allowing them to escape host immune surveillance, leading to the failure of conventional treatments. This paper reviews the definition, characteristics, and immune evasion mechanisms of CSCs, including immune checkpoint pathways, immunosuppressive microenvironment, and changes in surface antigen expression. Additionally, it explores various immunotherapies targeting CSCs, such as immune checkpoint inhibitors, CAR-T cell therapy, tumor vaccines, and other emerging therapies, discussing their research progress and clinical application prospects. By comprehensively understanding the immune evasion mechanisms of CSCs and related immunotherapies, we aim to provide new insights and strategies for future cancer treatments.

Keywords: Cancer Stem Cells, Immune Evasion Mechanisms, Immune Checkpoints, CAR-T Cell Therapy.

1. Introduction

Cancer Stem Cells (CSCs), a group of cells with self-renewal and multi-lineage differentiation potential, play a pivotal role in tumor initiation, progression, metastasis, and recurrence. In recent years, numerous studies have shown that CSCs not only escape conventional treatments such as chemotherapy and radiotherapy but also possess significant immune evasion capabilities, enabling them to avoid host immune surveillance and greatly increasing the difficulty of cancer treatment. Investigating the immune evasion mechanisms of CSCs and related immunotherapies is of paramount clinical significance. Understanding these mechanisms can provide a theoretical basis for developing new cancer treatments. Currently, immunotherapies targeting CSCs, such as immune checkpoint inhibitors, CAR-T cell therapy, and tumor vaccines, have shown promising clinical application prospects. Systematically summarizing and analyzing the progress of these immunotherapies can help promote their clinical application, ultimately improving the treatment outcomes and survival rates of cancer patients. This paper aims to systematically review the definition, characteristics, and immune evasion mechanisms of CSCs and explore the research progress of various immunotherapies related to CSCs. Through this research, we hope to provide new insights and strategies for future cancer treatments and promote the development of cancer immunotherapy.

2. Basic Concepts of Cancer Stem Cells

2.1. Definition of Cancer Stem Cells

Cancer Stem Cells (CSCs) are a class of cells with self-renewal and multi-lineage differentiation potential, believed to be the root cause of tumor heterogeneity and recurrence. CSCs possess characteristics similar to normal stem cells, including unlimited proliferative capacity, potential to differentiate into various cell types, and the ability to repair damage. However, unlike normal stem cells, CSCs exhibit tumor-promoting characteristics, maintaining tumor growth, metastasis, and recurrence within the tumor microenvironment. CSCs were first discovered in acute myeloid leukemia and have since been identified in various solid tumors, such as breast cancer, colorectal

cancer, and glioblastoma[1]. CSCs are typically identified and isolated using specific cell surface markers such as CD44, CD133, and ALDH1. Research indicates that CSCs play a central role in tumor formation and progression, and their resistance to traditional treatments and immune evasion capabilities make them crucial targets in cancer therapy. Therefore, in-depth research into the biological characteristics and functions of CSCs is essential for developing more effective cancer treatment strategies.

2.1. Characteristics of Cancer Stem Cells

Cancer Stem Cells (CSCs) have a range of unique biological characteristics that play a critical role in tumorigenesis, progression, and recurrence. Firstly, CSCs possess self-renewal capability. Through symmetric or asymmetric division, CSCs can continuously self-renew, maintaining their stem cell pool, allowing them to survive long-term in the tumor microenvironment and contribute to tumor recurrence post-treatment. Secondly, CSCs have multi-lineage differentiation potential, enabling them to differentiate into various tumor cell types, leading to tumor heterogeneity. This heterogeneity causes different treatment responses within the tumor, increasing treatment complexity and difficulty. Additionally, CSCs exhibit significant resistance to traditional chemotherapy and radiotherapy due to the high expression of drug efflux pumps (such as ABC transporters), robust DNA repair mechanisms, and a relatively quiescent cell cycle that avoids the effects on rapidly dividing cells. CSCs also activate anti-apoptotic mechanisms through various signaling pathways (e.g., PI3K/AKT, Wnt, and Notch), allowing survival in harsh microenvironments, making them difficult to eliminate by treatment[2]. Furthermore, CSCs exhibit immune evasion capabilities by downregulating major histocompatibility complex (MHC) molecules, secreting immunosuppressive factors, and inducing regulatory T cells (Tregs) to evade host immune surveillance, enhancing their survival and proliferation. Additionally, CSCs secrete angiogenic factors (e.g., VEGF) to promote tumor vascular formation, providing necessary nutrients and oxygen for tumor growth, facilitating invasion and metastasis. In summary, these characteristics of CSCs not only play a critical role in tumor growth and progression but also present significant challenges in current cancer treatment. Therefore, in-depth research into the biological characteristics of CSCs is crucial for developing new treatment strategies and improving cancer treatment outcomes.

2.2. Markers of Cancer Stem Cells

Identifying and isolating Cancer Stem Cells (CSCs) is crucial for studying their biological characteristics and functions. Researchers use a series of specific cell surface markers to achieve this goal. As shown in Table 1, different tumor types have specific CSC markers and their associated functions. These markers not only help distinguish CSCs from other tumor cells but also provide potential therapeutic targets[3].

Table 1: CSC Markers in Different Tumor Types and Their Functions

umor Type	Marker	Function and Role
Breast Cancer	CD44	Cell adhesion, migration, and signal transduction, associated with stem cell-like properties and drug resistance
Colorectal Cancer	CD133	Enhances tumor-forming ability and treatment resistance
Glioblastoma	CD133	Promotes tumor growth and recurrence
Liver Cancer	ALDH1	Self-renewal and differentiation potential, high drug resistance
Pancreatic Cancer	EpCAM	Cell adhesion molecule, associated with tumor invasion and metastasis

Firstly, CD44 is a transmembrane glycoprotein widely present in CSCs across various tumor types. CD44 is involved in cell adhesion, migration, and signal transduction, playing a vital role in tumor

invasion and metastasis. Cells with high CD44 expression are believed to have stem cell-like properties and are associated with tumor resistance and recurrence.Secondly, CD133 (Prominin-1) is another important CSC marker, initially discovered in glioblastoma stem cells and later validated in various tumors such as colorectal cancer, liver cancer, and lung cancer. CD133-positive cells exhibit stronger tumor-forming abilities and treatment resistance, making it a critical tool in CSC research and therapy.Additionally, ALDH1 (Aldehyde Dehydrogenase 1) is a commonly used CSC marker. ALDH1 is an enzyme involved in the cellular oxidative stress response, with high expression closely related to CSCs' self-renewal and differentiation potential. Studies show that cells with high ALDH1 expression have strong tumorigenic abilities and higher tolerance to chemotherapy drugs in various tumors.Other markers like EpCAM (Epithelial Cell Adhesion Molecule), CD24, and CD90 have also been reported in CSCs of different tumor types. Using a combination of these markers allows for more accurate identification and isolation of cells with stem cell properties, providing a powerful tool for CSC research.In summary, CSC markers are of great significance in cancer research and therapy. By studying these markers, researchers can gain deeper insights into the biological characteristics of CSCs and develop targeted therapeutic strategies for more effective cancer treatments.

3. Immune Evasion Mechanisms of Cancer Stem Cells

The immune evasion mechanisms of Cancer Stem Cells (CSCs) are key factors in their long-term survival and promotion of tumor progression within the tumor microenvironment. CSCs employ various strategies to evade recognition and attack by the host immune system. Firstly, CSCs often downregulate the expression of major histocompatibility complex (MHC) molecules, reducing antigen presentation and escaping immune surveillance. Additionally, CSCs secrete immunosuppressive cytokines, such as Transforming Growth Factor-β (TGF-β) and Interleukin-10 (IL-10), which inhibit the functions of T cells and natural killer (NK) cells and induce the generation of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), creating an immunosuppressive microenvironment. CSCs also highly express immune checkpoint molecules PD-L1 and CTLA-4, which bind to corresponding receptors on T cells, inhibiting their activation. Furthermore, CSCs interact with tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs), further enhancing immunosuppressive effects. Through these mechanisms, CSCs successfully evade immune surveillance and attacks, maintaining their survival and proliferation within tumors. Understanding these mechanisms is crucial for developing effective immunotherapies targeting CSCs[4].

4. Immunotherapies Targeting Cancer Stem Cells

4.1. Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) are a class of immunotherapies that have made significant advancements in cancer treatment in recent years by relieving the inhibition of the immune system by tumor cells, thereby enhancing the host's anti-tumor immune response. ICIs have also shown potential therapeutic effects against Cancer Stem Cells (CSCs).Firstly, Programmed Death-1 (PD-1) and its ligand PD-L1 are the most extensively studied immune checkpoints. CSCs often inhibit T cell activation and function by expressing high levels of PD-L1, thereby evading the immune system. PD-1/PD-L1 inhibitors block the interaction between PD-1 and PD-L1, restoring T cell activity and enhancing their ability to kill CSCs. For instance, PD-1 inhibitors such as Nivolumab and Pembrolizumab have shown good efficacy in various solid tumors and have been widely used.Secondly, Cytotoxic T-Lymphocyte-Associated Antigen-4 (CTLA-4) is another important immune checkpoint. CSCs also inhibit T cell activation by expressing high levels of CTLA-4. CTLA-4 inhibitors, such as Ipilimumab, block the CTLA-4 signaling pathway, enhancing T cell anti-tumor activity. Some studies have shown that combining CTLA-4 inhibitors with PD-1 inhibitors has a synergistic anti-tumor effect, especially in tumors resistant to single inhibitors.Additionally, other emerging immune checkpoints such as TIGIT, LAG-3, and TIM-3 are becoming research hotspots.

The expression and regulatory mechanisms of these checkpoints in CSCs are being explored to develop more effective treatment strategies. For example, TIGIT inhibitors block the interaction between TIGIT and its ligand, restoring the functions of effector T cells and NK cells and enhancing their ability to kill CSCs.Although ICIs have made significant progress in cancer treatment, there are still challenges in treating CSCs. The heterogeneity and complexity of the CSC microenvironment mean that single ICIs may not completely eliminate CSCs. Future research should focus on the combined application of multiple ICIs and the integration of other treatments (such as CAR-T cell therapy and tumor vaccines) to achieve better therapeutic effects.In summary, ICIs enhance the host's anti-tumor immune response by relieving CSC-mediated immune suppression, demonstrating great potential in treating CSCs. Understanding and overcoming existing challenges will help further improve the clinical application of this therapy[5].

4.2. CAR-T Cell Therapy

Chimeric Antigen Receptor T-Cell (CAR-T) therapy is a revolutionary cancer immunotherapy that uses genetic engineering to modify a patient's T cells to express specific antigen receptors, thereby precisely identifying and killing tumor cells. CAR-T cell therapy targeting Cancer Stem Cells (CSCs) shows great potential and challenges.Firstly, the basic principle of CAR-T cell therapy is to introduce genes encoding specific antigen receptors into a patient's T cells, enabling these modified T cells to recognize specific antigens on the surface of tumor cells and accurately attack them. For CSCs, ideal targets should have high specificity to avoid attacking normal cells. CSC markers such as CD44, CD133, and EpCAM have become important targets for designing CAR-T cells. For instance, CAR-T cells targeting CD133 have shown good anti-tumor effects in some preclinical studies, effectively recognizing and eliminating CD133-expressing CSCs.Secondly, a major advantage of CAR-T cell therapy is its high specificity and powerful killing ability. Modified CAR-T cells can proliferate extensively in the body and persist, providing sustained anti-tumor effects. However, CAR-T therapy targeting CSCs also faces numerous challenges. CSCs have high heterogeneity and plasticity, allowing them to evade immune recognition by altering surface antigen expression. Additionally, the tumor microenvironment in which CSCs reside is often strongly immunosuppressive, affecting the activity and persistence of CAR-T cells.To overcome these challenges, researchers are exploring various improvement strategies. For example, bispecific or multispecific CAR-T cells can recognize multiple CSC markers simultaneously, reducing the possibility of CSC evasion. Enhanced CAR-T cells incorporate costimulatory signals such as CD28 or 4-1BB into their structure, boosting their proliferative capacity and anti-tumor activity. Additionally, combining CAR-T cells with other immunotherapies, such as immune checkpoint inhibitors, further enhances CAR-T cell efficacy in immunosuppressive microenvironments.Although CAR-T cell therapy targeting CSCs is still in the research and development stage, its strong potential demonstrated in preclinical studies makes it a promising future direction for cancer treatment. With technological advancements and deeper understanding of CSC biology, CAR-T cell therapy is expected to achieve breakthroughs in clinical applications, providing more precise and effective treatment for cancer patients.In summary, CAR-T cell therapy offers new hope for treating CSCs through its high specificity and powerful killing ability. Future research should focus on optimizing CAR-T cell design and enhancing their activity and persistence in complex tumor microenvironments to achieve better clinical outcomes[6].

5. Research Progress in Immunotherapy for Cancer Stem Cells

5.1. Preclinical Research

Preclinical research plays a crucial role in advancing immunotherapy for Cancer Stem Cells (CSCs). These studies are primarily conducted in laboratories and animal models, aiming to explore the immune evasion mechanisms of CSCs, evaluate the efficacy and safety of new immunotherapies, and lay the foundation for clinical trials.Firstly, immune checkpoint inhibitors targeting CSCs have made significant progress in preclinical studies. Research has shown that CSCs can effectively evade T

cell-mediated immune attacks by highly expressing checkpoint proteins such as PD-L1 and CTLA-4. By using PD-1/PD-L1 and CTLA-4 inhibitors, researchers have observed significantly enhanced T cell activity and markedly reduced CSC survival rates in various tumor models. For example, in breast cancer and glioblastoma models, PD-1 inhibitors significantly reduced the number of CSCs and extended the survival of animals.Secondly, CAR-T cell therapy has demonstrated strong potential against CSCs in preclinical research. Researchers have engineered CAR-T cells targeting CSC surface markers such as CD44, CD133, and EpCAM and validated their effects in various tumor models. These CAR-T cells can recognize and kill CSCs in vivo, inhibiting tumor growth and metastasis. For instance, in colorectal and liver cancer models, CD133-targeted CAR-T cells showed significant anti-tumor activity, effectively eliminating CSCs and reducing the risk of tumor recurrence.Additionally, tumor vaccines as a strategy to activate the host immune system to attack CSCs have also made progress in preclinical studies. Researchers have developed various tumor vaccines based on CSC antigens, aiming to induce specific immune responses. For example, vaccines prepared using CSC-related antigens such as SOX2, OCT4, and NANOG significantly enhanced T cell and B cell activity, reduced tumor burden, and improved survival rates in mouse tumor models.Other emerging immunotherapies, such as NK cell therapy and immune modulators, have also shown potential against CSCs in preclinical studies. NK cells can directly kill CSCs by recognizing abnormal antigens on their surface. In contrast, immune modulators can restore the immune system's surveillance function against CSCs by modulating the tumor microenvironment.Despite the many advances in preclinical research, these therapies still face challenges in practical application. The heterogeneity of CSCs, the complexity of the tumor microenvironment, and the diversity of immune evasion mechanisms all pose challenges to the efficacy of immunotherapy. Therefore, future research needs to further optimize these therapies, explore combination treatment strategies, and validate their efficacy and safety in more complex models.In summary, preclinical research provides a solid foundation for the development of immunotherapy for cancer stem cells. By deeply understanding the biological characteristics and immune evasion mechanisms of CSCs, researchers continuously optimize and innovate immunotherapies, striving to bring new breakthroughs and hope to clinical applications[7].

5.2. Clinical Trials

Clinical trials are crucial for verifying the safety and efficacy of Cancer Stem Cell (CSC) immunotherapies in humans. As shown in Table 2, with significant advancements in CSC-related immunotherapies in preclinical research in recent years, an increasing number of clinical trials are underway to evaluate the performance of these innovative therapies in actual clinical applications.

Table 2: Progress of Clinical Trials for CSC Immunotherapies

Immunotherapy Type	Trial Name and Number	Indication	Clinical Trial Phase	Main Findings and Effects
Immune Checkpoint Inhibitors	Nivolumab (CheckMate)	Non-Small Cell Lung Cancer	Phase III	Improved progression-free survival (PFS) and overall survival (OS)
Immune Checkpoint Inhibitors	Pembrolizumab (KEYNOTE)	Melanoma	Phase III	Significantly reduced CSCs, delayed tumor progression
CAR-T Cell Therapy	CD133-CAR-T (NCT02541370)	Advanced Liver Cancer	Phase I/II	Preliminary anti-tumor activity, good tolerance
Tumor Vaccines	SOX2 Vaccine (NCT03047837)	Pancreatic Cancer	Phase I	Induced specific immune responses, reduced tumor burden in some patients
NK Cell Therapy	NK-92 (NCT00909558)	Various Solid Tumors	Phase I/II	Showed preliminary efficacy, good safety

Firstly, immune checkpoint inhibitors have shown initial success in clinical trials targeting CSCs. PD-1 and PD-L1 inhibitors, such as Nivolumab and Pembrolizumab, have demonstrated certain efficacy in various solid tumors. Studies have shown that these inhibitors can enhance T cell activity, reduce the number of CSCs, and delay tumor progression. For instance, the use of PD-1 inhibitors in non-small cell lung cancer and melanoma patients significantly improved progression-free survival (PFS) and overall survival (OS). However, the specific efficacy against CSCs still requires further exploration and verification.Secondly, CAR-T cell therapy has also shown strong potential in clinical trials. Although CAR-T therapy is currently mainly applied to hematologic malignancies such as acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL), CAR-T therapy targeting CSCs is gradually expanding into solid tumors. Several early clinical trials have shown that CAR-T cells targeting CSC markers such as CD133 and EpCAM have potential efficacy in certain solid tumor patients. For example, in a clinical trial for advanced liver cancer, CD133-CAR-T cells demonstrated good tolerance and preliminary anti-tumor activity. However, the application of CAR-T therapy in solid tumors still faces many challenges, such as immune suppression in the tumor microenvironment and the persistence of CAR-T cells, requiring further research and optimization.Additionally, the application of tumor vaccines in clinical trials is gradually unfolding. Vaccines prepared from CSC-related antigens (such as SOX2, OCT4, and NANOG) have been evaluated in early clinical trials for various tumor types[8]. Results show that these vaccines can induce specific immune responses, enhance T cell and B cell activity, reduce tumor burden in some patients, and improve quality of life. For example, in pancreatic cancer patients, CSC antigen vaccines showed certain immune responses and disease control rates. However, vaccine efficacy varies among individuals and requires further validation in larger-scale and multicenter clinical trials.Other emerging immunotherapies, such as NK cell therapy and immune modulators, are also undergoing clinical trials to evaluate their potential against CSCs. NK cell therapy directly recognizes and kills CSCs, showing preliminary efficacy in some trials. In contrast, immune modulators restore immune surveillance against CSCs by altering the tumor microenvironment, achieving positive results in some patients.Although clinical trials of CSC immunotherapies show promising prospects, many challenges remain. Issues such as CSC heterogeneity, the complexity of the tumor microenvironment, treatment specificity, and side effects need to be further addressed in future research. With advancements in science and technology and a deeper understanding of CSC biology, these therapies are expected to play a more significant role in future cancer treatment.In summary, clinical trials are crucial for verifying the effectiveness and safety of CSC immunotherapies. Through continuous optimization and innovation, these therapies are expected to provide more precise and effective treatment options for cancer patients, improving their survival rates and quality of life.

5.3. Research Achievements and Challenges

Immunotherapy for Cancer Stem Cells (CSCs) has made significant progress in recent years, but it also faces many challenges. The following is a comprehensive analysis of current research achievements and challenges.Firstly, in terms of research achievements, immune checkpoint inhibitors have made significant progress in treating CSCs. By blocking the PD-1/PD-L1 and CTLA-4 pathways, these inhibitors can restore T cell anti-tumor activity, showing good efficacy in various solid tumors. For example, PD-1 inhibitors Nivolumab and Pembrolizumab have significantly improved progression-free survival (PFS) and overall survival (OS) in non-small cell lung cancer and melanoma patients. These results indicate that immune checkpoint inhibitors can effectively target CSCs and improve cancer treatment outcomes.Secondly, CAR-T cell therapy has shown strong potential against CSCs in both preclinical and clinical research. CAR-T cells targeting CSC surface markers (such as CD133 and EpCAM) have demonstrated significant anti-tumor activity in various tumor models and initial efficacy in some solid tumor patients. For instance, in clinical trials for advanced liver cancer, CD133-CAR-T cells not only showed good tolerance but also exhibited certain anti-tumor activity. These research achievements provide important evidence for the application of CAR-T cell therapy in solid tumors.Additionally, tumor vaccines have also made progress in CSC research. Vaccines prepared from CSC antigens (such as SOX2, OCT4, and NANOG) have induced

specific immune responses in early clinical trials, reducing tumor burden and improving quality of life in some patients. For example, CSC antigen vaccines showed certain immune responses and disease control rates in pancreatic cancer patients, providing new treatment ideas.However, despite the significant progress, CSC immunotherapy still faces many challenges. Firstly, CSC heterogeneity is a major obstacle. CSCs exhibit significant differences in characteristics among different tumor types and patients, making it difficult for a single therapy to comprehensively cover and effectively eliminate CSCs. Researchers need to develop combination therapies targeting multiple markers and mechanisms to address CSC heterogeneity.Secondly, the complexity of the tumor microenvironment is another challenge. The tumor microenvironment where CSCs reside is often highly immunosuppressive, affecting the efficacy of immunotherapy. For example, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) play important roles in the tumor microenvironment, inhibiting the functions of effector T cells and CAR-T cells. Effectively modulating the tumor microenvironment to enhance immunotherapy efficacy is a pressing issue to be resolved in clinical practice.Furthermore, the side effects and safety of immunotherapy are also important considerations. While immune checkpoint inhibitors and CAR-T cell therapy activate the immune system, they may trigger autoimmune reactions, leading to severe immune-related adverse events (irAEs). Researchers need to further optimize these therapies to improve their specificity and safety and reduce the occurrence of side effects.In conclusion, although CSC immunotherapy has achieved significant results in research, its clinical application still faces many challenges. Future research should focus on addressing CSC heterogeneity and the complexity of the tumor microenvironment, optimizing immunotherapy design and combination strategies to improve efficacy and safety, and providing more effective treatment options for cancer patients.

6. Conclusion

Cancer Stem Cells (CSCs) play a crucial role in tumor initiation, progression, metastasis, and recurrence. Their characteristics, including self-renewal, multi-lineage differentiation, drug resistance, and immune evasion, make traditional treatments insufficient for complete tumor eradication. Immunotherapies targeting CSCs, such as immune checkpoint inhibitors, CAR-T cell therapy, and tumor vaccines, show great promise but also face challenges related to heterogeneity and the complexity of the tumor microenvironment. Future research should focus on developing combination therapies and optimizing immunotherapy design to improve efficacy and safety. Continuous research and innovation are expected to lead to breakthroughs in cancer treatment, providing more precise and effective therapeutic options for patients.

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