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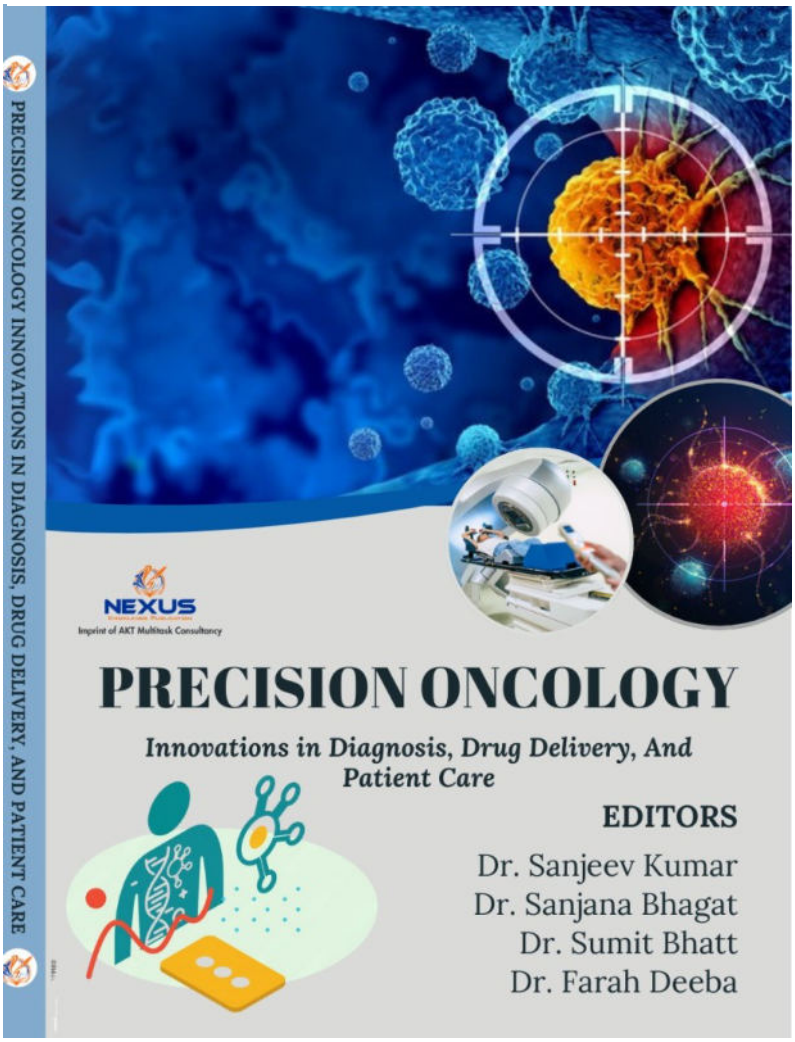
Precision Oncology: Innovations in Diagnosis, Drug Delivery, And Patient Care



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Chapter- 7

IMMUNOTHERAPY IN THE PRECISION ERA

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Immunotherapy has revolutionized cancer treatment where the immune system of the body is used to combat tumors and the immune checkpoint inhibitors (ICIs) have been at the center stage. To avoid immune surveillance, tumors use the PD-1/PD-L1 and CTLA-4 checkpoint pathways that inhibit T-cells. The drugs that help to restore the activity of T-cells include pembrolizumab, nivolumab, atezolizumab (PD-1/PD-L1 inhibitors), and ipilimumab (CTLA-4 inhibitor), which help to prolong the life of some cancers like melanoma, lung cancer, and urothelial carcinoma. Nevertheless, this is not applicable to all patients and predictive biomarkers are essential in-patient selection. Underlying biomarkers are PD-L1 level, tumor mutational load (TMB), and microsatellite instability-high (MSI-H) that can detect more responsive tumors with respect to ICIs.

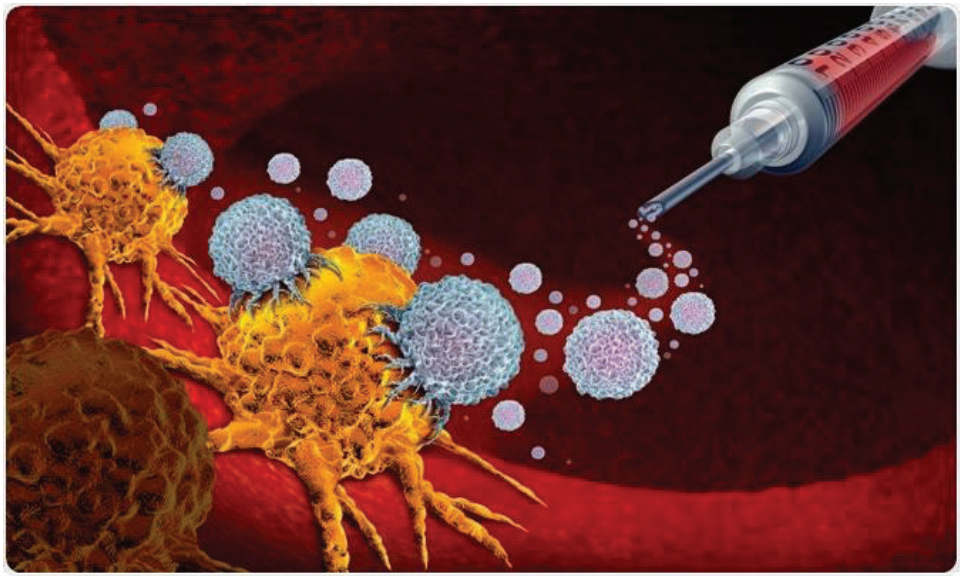

Figure 1: Immunotherapy

Source: (https://www.news-medical.net/health/What-is-Immunotherapy.aspx)

Other than ICIs, tumor-specific neoantigen-targeted personalized cancer vaccines are emerging. These therapeutic vaccines, unlike preventive vaccines, are meant to cause the development of specific immune response against cancer cells. Examples of platforms are peptide-based vaccines, mRNA vaccines, and dendritic cell (DC) vaccines each of which is aimed at presenting neoantigens to the body to stimulate cytotoxic T-cells. Clinical results have been positive, particularly in melanoma and glioblastoma, and vaccines are commonly used hand in hand with ICIs to improve effect.

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Adaptive cell therapies (ACT) including CAR-T and TCR-T cell therapies take the field of personalized immunotherapy a step further by engineering or clustering patient-derived T-cells to target tumor antigens. CAR-T treatment has been exceptionally effective in hematologic malignancies, especially with CD19-targeted therapies, with TCR-T treatment potentially extending to solid tumors as the range of targets can include intracellular antigens. Although breakthroughs were made, issues such as cytokine release syndrome, neurotoxicity, antigen heterogeneity and solid tumor barriers have limited the broader use.

One of the biggest challenges of all immunotherapies is its ability to forecast the patients who are going to respond. Lack of precision is caused by tumor heterogeneity, dynamic tumor micro environments, and incomplete biomarkers. Although PD-L1 and TMB inform therapy, they have limitations that highlight the necessity of superior predictive instruments. Future prospects would be the integration of multi-omics, predictive modeling with AI and rational combination therapies to reprogram the tumor microenvironment, circumvent resistance, and expand patient response. Combined, these advances are leading the new wave of personalized cancer immunotherapy.

7.1. IMMUNE CHECKPOINT INHIBITORS AND PREDICTIVE BIOMARKERS

The use of immunotherapy in cancer therapy has brought a new twist in the treatment process in the sense that it uses the immune system of the patient to identify and eliminate the malignant cells. Although the immune system is inherently competent to respond to abnormal cells through detection and destruction, tumors usually develop ways of avoiding immune surveillance. One of the most important approaches is to take advantage of the immune checkpoints to control the immune system of self-tolerance and suppress excessive activation of the immune system. With the help of them, the T-cells can be successfully silenced by the tumors, and the cancer cells may develop uncontrolled growth and spread. Immune checkpoint inhibitors (ICIs) are medicines that prevent these inhibitory processes and instead rejuvenate T cells to allow the immune system to spearhead an organized assault on cancerous cells.

Based on the evidence that ICIs are not effective in all patients and tumor types, predictive biomarkers that facilitate treatment should not be ignored. PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI) can be used as a biomarker to select patients with the highest likelihood of respondence to checkpoint blockade therapy. Improving immunotherapy by including biomarker testing in clinical practice can enable the oncologist to

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optimally personalize the treatment to maximize efficacy and minimize exposure to unnecessary side effects. This treatment strategy is a combination of immune checkpoint inhibition and accurate patient selection based on specific biomarkers, which can get as much therapeutic benefit as possible and is one of the foundations of contemporary precision oncology.

❖ ***Immune Checkpoint Inhibitors (ICIs)***

1. **PD-1/PD-L1 Inhibitors:** Programmed cell death protein 1 (PD-1) is a T-cell receptor and the ligand is PD-L1 expressed on many tumor cells. In case of PD-1 PD-L1 binding, T-cell activity is inhibited, and tumor cells escape immunodetection. Pembrolizumab, nivolumab and atezolizumab block PD-1, PD-L1, and therefore restore T-cell functions to treat tumor cells. Those treatments are effective against various cancers, such as melanoma, lung cancer, and urothelial carcinoma.

2. **CTLA-4 Inhibitors:** Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another checkpoint molecule on T-cells that modulates immune-activation mainly in lymph nodes in the priming step of T-cell responses. A CTLA-4 inhibitor, ipilimumab, hampers this checkpoint, resulting in an augmentation of T-cell activation and proliferation, which raises the capacity of the immune system to assail tumor cells. CTLA-4 inhibitors have demonstrated significant efficacy in cancerous diseases that are highly immunogenized, including melanoma.

❖ ***Predictive Biomarkers***

Identifying patients likely to benefit from ICIs is crucial, as not all tumors respond equally to immunotherapy. Predictive biomarkers help guide patient selection and optimize treatment outcomes:

1. **PD-L1 Expression:** Tumors expressing high levels of PD-L1 are often more responsive to PD-1/PD-L1 inhibitors. Immunohistochemistry tests quantify PD-L1 on tumor or immune cells, helping clinicians determine the likelihood of therapeutic success.

2. **Tumor Mutational Burden (TMB):** TMB measures the total number of mutations within a tumor's genome. Tumors with high TMB generate more neoantigens, which are recognized as foreign by the immune system, enhancing the efficacy of ICIs. High TMB has been associated with better responses in lung cancer, melanoma, and other solid tumors.

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3. **Microsatellite Instability-High (MSI-H):** Tumors with defective DNA mismatch repair exhibit MSI-H, resulting in a high rate of mutations and increased neoantigen formation. MSI-H tumors are particularly sensitive to ICIs because their abnormal proteins make them more visible to the immune system. This biomarker is commonly used to guide immunotherapy in colorectal and other gastrointestinal cancers.

7.2. PERSONALIZED CANCER VACCINES AND NEOANTIGEN TARGETING

Individualized cancer vaccines constitute the latest methodology in immunotherapy where the goal is to use the body of a patient with regard to its immune system to specifically target and eliminate cancer cells. Contrary to conventional preventive vaccines, which guard against infection, therapeutic cancer vaccines are developed to treat pre-existing cancer tumors by prompting powerful and specific anti-tumor immunity. These vaccines stimulate T cells to attack cancer cells but not normal tissue by introducing the immune system to tumor-associated antigens, and this attack is less destructive than that of other usual therapies because it destroys the cancer and not normal tissue. The method makes the immune system a patient-specific tool against cancer that is highly accurate.

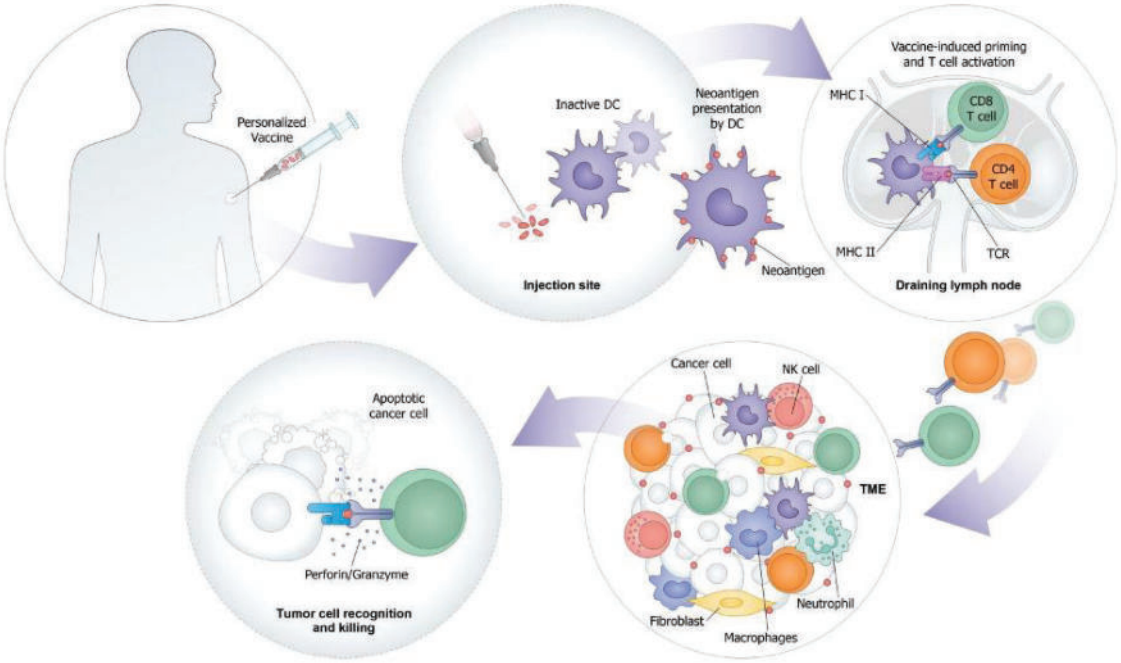

Figure 2: Personalized Cancer Vaccines

Source: (https://www.mdpi.com/1422-0067/24/23/16591)

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Recent developments in genomic sequencing, bioinformatics and immunogenomics have enabled the development of vaccines that can be targeted to the individual genes of tumor. The foundational component of this strategy is that of neoantigens, new protein sequences that are products of tumor-specific mutation, which are non-existent in normal tissues. Neoantigens are extremely specific to the tumor of a specific patient, so by targeting them, it is possible to activate the immune in the most specific manner possible, reducing the chances of autoimmune reactions and increasing the effects of the therapy. Not only do personalized cancer vaccines mark an important advance towards personalized immunotherapy, but also have potential to be combined with other precision therapies, including checkpoint inhibitors, to enhance response rates and long-term outcomes in cancer therapy.

Neoantigen-Based Vaccines

Neoantigen-based vaccines are one of the most recent approaches to cancer immunotherapy based on the ability to capitalize on individual tumor mutational landscapes. Neoantigens are new peptide sequences that are produced due to tumor specific mutation, including single nucleotide variants, insertions, deletions, or fusions of genes. Since these antigens are not present in normal tissues, they are not immunologically regulated by central tolerance and are very immunogenic with high chances of not causing autoimmunity. This attribute provides them with a clear cut above conventional tumor-associated antigens that are commonly expressed on normal tissues and will result in less vigorous or less specific immune action.

Having added tumor-specific neoantigens to vaccine preparations, scientists hope to induce and expand populations of T-cells with stunning specificity against cancer cells. After vaccination, dendritic cells load the neoantigen peptides onto the MHC system, which activates the cytotoxic Cy8+ T-cells and helper CD4+ T-cells, which are both essential in coordinating anti-tumor immunity. Such a specific method increases the awareness of tumor cells and their destruction, with a lower level of collateral damage to the normal tissues.

Various vaccine systems are under use as neoantigen delivery systems and they include, synthetic peptide-based vaccines, RNA based vaccines, viral vectors and dendritic cell based vaccines. The platforms have different strengths in the aspects of immunogenicity, scalability and production speed. Recent discoveries in next-generation sequencing (NGS) and bioinformatics-based neoantigen prediction algorithms have made the discovery of patient-specific neoantigens faster, and it is now possible to design highly personalized vaccines within clinically relevant timelines.

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There is promising evidence of efficacy given by clinical trials. Indicatively, neoantigen melanoma vaccines have been able to trigger strong T-cell responses that are associated with progression-free survival. There, too, initial work in glioblastoma and non-small cell lung cancer has revealed promising evidence of immune response and tumor regression. In addition, neoantigen vaccines regimens have been used in combination with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 therapies) with an enhanced ability to generate antitumor effect by reversing T-cell exhaustion and immune suppression in the tumor microenvironment.

In spite of their promise, there are a number of challenges. The design of neoantigen-based vaccines is resource- and time-consuming since it involves custom sequencing, computational forecasting, and vaccine production. Besides, the heterogeneity of tumors and the possibility of evolution of tumor cells and loss of targeted neoantigens are obstacles to long-term efficacy. However, the accuracy, specificity, and safety profile of neoantigen-based immunotherapy makes them one of the most promising frontiers to the personalized treatment of cancer, and the possibilities of this technology to change treatment regimens in different malignancies.

- **Types of Personalized Cancer Vaccines:**

1. **Peptide-Based Vaccines:** It consists of tumor neoantigens produced as short synthetic peptides. They are then introduced into the patient by the major histocompatibility complex (MHC) molecules, which activate an immune response against the tumor, upon their introduction. They can be comparatively manufactured and they might need adjuvants to enhance immune responses.

2. **mRNA Vaccines:** mRNA vaccines are the latest and a potent platform, in which neoantigens are encoded, giving the patient their own cells to manufacture and present them to the immune system. The method allows scaling and quick customization. After the mRNA vaccines demonstrated success in infectious diseases (e.g. COVID-19), their use in cancer has become increasingly popular with mRNA vaccines demonstrating effectiveness in melanoma, glioblastoma, and other tumors.

3. **Dendritic Cell (DC) Vaccines:** Dendritic cells are professional antigen-presenting cells that are able to prime strong T-cell responses. Under the process, dendritic cell are cloned and removed out of the patient, loaded with tumor neoantigens (peptides, RNA or tumor lysates), and returned. This augments T-cell activation and produces a stronger antitumor immune response.

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Clinical Significance

Cancer vaccines Personalized cancer vaccines are an emerging immunotherapeutic modality aiming to induce the patient or his/her own immune system to identify and kill tumor-specific antigens, especially those found with somatic mutations as neoantigens. These vaccines are being clinically pursued in a broad range of clinical trials and have demonstrated promising results, particularly in highly mutated cancers like melanoma, glioblastoma and non-small cell lung cancer (NSCLC). Neoantigens are highly concentrated in these tumours offering a good target to be taken up by immunity without posing a risk of off-target toxicities.

Initial preclinical studies have shown that personalized vaccines can effectively result in robust and durable T-cell responses, which are typically associated with clinical outcomes like tumor regression, slowed progression or extended survival. Notably, the given vaccines are not produced as monotherapy but are being progressively used together with immune checkpoint inhibitors (e.g. anti-PD-1/PD-L1 and anti-CTLA-4 antibodies) to conquer the intensive immunosuppressive processes within the tumor microenvironment (TME). These combinations have also led to synergistic effects, increasing the persistence of vaccine-primed T-cells by reducing T-cell exhaustion and into a durable and clinically meaningful response.

Clinical relevance of personalized cancer vaccines goes beyond the therapeutic effect. They are a paradigm shift to precision medicine when the therapies are specific to the mutational profile or the specific tumor in a person. It is not only more efficacious but also lowers the chances of systemic toxicities as opposed to conventional chemotherapies or generalized immunotherapies. In addition, current developments in next generation sequencing, bioinformatics pipelines, and algorithmic neoantigens predictive methods are cutting down the vaccine design and manufacturing schedules, and these therapies are becoming more practical to implement into practice.

Although there are obstacles including the expense and time involved in designing personalized vaccines, the inconsistency of immune competence across patients, and difficult amino acid combinations to predict as really immunogenic neoantigens, the accumulating clinical data overwhelmingly points to their potential. When optimized, personalized cancer vaccines have the potential to be an essential part of the next-generation oncology, providing the patient with the option to treat cancer with durable, highly specific, and less toxic treatment and personalized cancer vaccines.

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7.3. ADOPTIVE CELL THERAPIES (CAR-T, TCR-T)

Adoptive Cell Therapy (ACT) is a game-changing technology in cancer therapy, which uses the immune system of the body to attack and kill malignant cells with great accuracy never seen before. At the heart of this strategy is the isolation of T-lymphocytes, be it off the peripheral blood of the patient or directly off the tumor microenvironment and activated and then expanded in vitro in the laboratory under controlled conditions. Such cells can be further modified to increase their anti-cancer property. Regarding Chimeric Antigen Receptor T-cell (CAR-T) therapy, T-cells are engineered to produce artificial receptors that target antigens on tumors that make them target and destroy cancer cells more efficiently. Likewise, T-cell receptor-engineered T-cell (TCR-T) therapy T-cells are modified to recognize the presence of particular peptides on tumor cell major histocompatibility complex molecules which increases their specificity and cytotoxicity to tumors. The reinfusion of these powerful, tumor-targeted immune cells into the patient may lead to a powerful anti-tumor response, even to the extent of complete remission, particularly in hematological malignancies, like acute lymphoblastic leukemia and in some cases of lymphomas that have become resistant to conventional treatment.

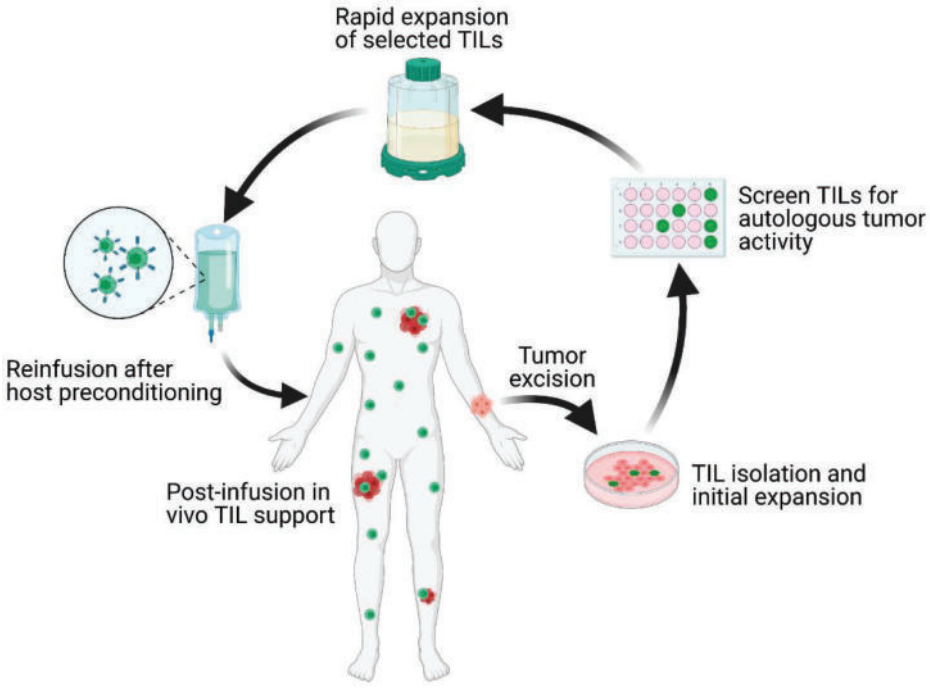

Figure 3: Adoptive Cell Therapy

Source: (https://www.mdpi.com/2073-4409/10/4/808)

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Types of ACT:

1. **CAR-T Cell Therapy (Chimeric Antigen Receptor T-cells)**

CAR-T cell therapy is among the most innovative and clinical success stories of adoptive cell therapy (ACT). In this method, the T-cells of a patient are harvested and genetically engineered ex vivo to produce chimeric antigen receptors (CARs)- artificial receptors to identify and attach to certain antigens on tumor cells. As opposed to natural T-cell receptors, CARs do not rely on major histocompatibility complex (MHC), which means that they can overcome tumor mechanisms aimed at avoiding immune rejection in the form of downregulating the major histocompatibility complex. The special characteristic of CAR-T cells enables them to be used effectively in antigen delivery against tumor-specific or tumor-associated antigens.

One of the most remarkable targets is CD19, which is persistently expressed in malignant B-cells in leukemias and lymphomas. Anti-CD19 CAR-T cell therapies have proven to be more successful than ever in blood cancers, especially in patients with refractory or relapsed disease that had exhausted all forms of conventional treatments, including chemotherapy, radiation and stem cell transplantation. Innovative FDA-approved therapies in this area are tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta). There have been impressive clinical trial

and real-world results such as high response rates in general and long-lasting remissions in patients who were considered untreatable.

The therapeutic benefit of CAR-T cells is not only in their capacity to cause a quick tumor clearance, but also in their possibility to be maintained in the human body over a long period and, thus, provide immunosurveillance and decrease the risk of the recurrence. Significantly, CAR-T therapy has revolutionized the management of pediatric and adult patients with B-cell acute lymphoblastic leukemia (ALL), and in adults with large B-cell lymphomas, and has established itself as an essential part of the treatment paradigm in treatment-resistant environment.

Outside of CD19, development of CAR-T applications is underway to incorporate other antigens like BCMA (B-cell maturation antigen) in multiple myeloma and CD22 in B-cell malignancies, which expands the therapeutic clinical program. Additionally, designs of CAR are being explored to counter resistance, improve on efficacy, and address toxicities such as cytokine release syndrome (CRS) and neurotoxicity via CAR-based innovations, including dual-target CARs, armored CAR-T cells that express cytokines and safety-switch systems.

Overall, CAR-T cell therapy has emerged as a shift in paradigm in cancer immunotherapy, providing sustained responses where traditional therapies have been unable, and platforming the development of next-generation engineered T-cell therapies to increase the spectrum of ACT into hematologic and, ultimately, solid tumor.

2. TCR-T Cell Therapy (T-cell Receptor Therapy)

Another sophisticated adaptive cell therapy (ACT) that is not similar to CAR-T treatment is TMC-T cell therapy. TCR-T therapy does not require the introduction of synthetic receptors but includes a genetic modification of T-cells of a patient to express tumor-specific T-cell receptors (TCRs). These engineered TCRs can identify intracellular tumor-associated antigens that are processed and shown on the tumor cell surface within major histocompatibility complex (MHC) molecules. This renders TCR-T therapy distinctly potent, since it increases the repertoire of possible targets beyond superficial antigens to a far broader one that encompasses both cancer-testis antigens (e.g., NY-ESO-1, MAGE-A3) and viral antigens in viral-related malignancies.

This is unlike CAR-T therapy, which is restricted to the ability to identify antigens on the surface of the cell, TCR-T therapy takes advantage of cell-native antigen-processing

mechanism. This implies that TCR-T cells are capable of recognizing and destroying tumor cells on the basis of intracellular protein fragments displayed by MHC molecules. Consequently, the method has specific potential in solid tumor therapy, in which appropriate surface antigens are scarce and antigen diversity is a significant concern.

TCR-T Therapy TCR-T therapy has shown promise in clinical trials in synovial sarcoma and multiple myeloma with tumor regression and long-lasting responses reported in early-phase trials (NYESO-1) with TCR-T therapy. Likewise, engineered TCRs targeting viral antigens, including the HPV E6 and E7 proteins have shown promise in HPV-related cervical and head-and-neck cancers. These results highlight the usefulness of TCR-T therapy in the treatment of both hematologic and solid cancers.

The benefits of TCR-T therapy are that it has wide antigen-binding properties and that it can penetrate intracellular tumor weaknesses inaccessible to CAR-T cells. Nonetheless, it is also associated with certain issues including rigid reliance on MHC-restricted antigen presentation, patient HLA proteomic variability and risk of off-target toxicities in case engineered TCRs cross-react with normal tissue antigens.

Regardless of these shortcomings, continued efforts in TCR affinity engineering, safety switch and customized approaches to HLA matching are enhancing the safety and effectiveness of TCR-T therapy. Collectively, these discoveries make TCR-T cell therapy a highly potential direction in the ACT landscape to complement CAR-T therapy, by expanding the therapeutic scope of most tumor types.

Challenges and Limitations of ACT

Despite the proven potential of adoptive cell therapy (ACT) in the transformative immunotherapy of cancer, there are various issues that still limit its wider clinical use. Cytokine Release Syndrome (CRS) is one of the most serious and possibly even life-threatening complications. CRS is caused by the huge discharge of pro-inflammatory cytokines in the aftermath of engaging engineered T-cells in tumor cells. In clinical terms, it presents itself as high fever, hypotension, hypoxia, dysfunction of multiple organs, which in extreme cases can result in death unless timely medical intervention is undertaken. The existing treatment methods, including the use of IL-6-blockers (e.g., tocilizumab) and corticosteroids, have resulted in better control; nevertheless, the challenge of suppressing the immune system without interfering with treatment efficacy is a fine balancing act.

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Neurotoxicity, which is also referred to as immune effector cell-associated neurotoxicity syndrome (ICANS) is another significant toxicity. The spectrum of neurological manifestations of this complication is quite broad and includes confusion, disorientation, seizures, cerebral edema, and encephalopathy. In contrast to CRS, the specific mechanisms of neurotoxicity remain not yet fully studied, but they may be the endothelial activation, the breakage of the blood-brain barrier, and the neuroinflammation caused by cytokines. Neurotoxicity is not predictable, which further complicates the treatment regimens of ACT.

Besides toxicities, ACT, and especially chimeric antigen receptor T-cell (CAR-T) therapies, have limited efficacy in solid tumors relative to hematological malignancies. This disparity can be explained by several biological and structural obstacles:

- **Immunosuppressive Tumor Microenvironment (TME):** The TME is full of the inhibitory cytokines (e.g., TGF-B, IL-10) and immune checkpoint proteins (e.g., PD-L1), which together inhibit T-cell activity and growth.
- **Physical Barriers:** The thick extracellular matrix and stromal architecture surrounding many solid tumors is physically associated with hindering T-cell infiltration and limiting their cytotoxic capability.
- **Heterogeneity of Antigen:** In contrast to hematological cancers, solid tumors are heterogeneously antigen-expressive. In the treatment process, the targeted antigens may be down-regulated or even lost by the tumor cells and this allows the tumor cells to escape immunity and eventually causes a relapse.

More so, the complexity of manufacturing, high cost and the logistic problems of producing patient specific engineered T-cells also restrict the universal access of ACT. The procedure involves harvesting of autologous T-cells, genetic engineering, cell culture in strict requirements and reinfusion in time, all of which is resource-consuming.

Collectively, these constraints suggest the necessity of next-generation design, such as enhancement of safety-switch designs to regulate toxicities, engineering T-cells with a better homing and infiltration potential, developing allogeneic off-the-shelf ACT products, and combining ACT with checkpoint blockade or oncolytic agents to overcome the immunosuppressive environment of solid tumors. It is only in response to these challenges that ACT can become a genuinely long-term and multi-modal therapeutic agent against a wide range of cancers.

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7.4. PRECISION CHALLENGES IN IMMUNOTHERAPY RESPONSE PREDICTION

Immunotherapy has transformed treatments in cancer, yet one of its greatest shortcomings is that it only a fraction of patients responds with durable meaningful responses. It is hard to predict that a patient will be benefited as both the tumor and the host immune system are highly heterogeneous and dynamic. Precision oncology is an innovative approach to personalize immunotherapy, but there are important obstacles that make response prediction difficult.

1. **Tumor Heterogeneity:** Cancers are not homogenous but are comprised of a number of subclones that have varying genetic and phenotypic profiles. In the same tumor, cells can contain target antigens that immunotherapy can recognize but others can have them or down-regulate them. Such clonal diversity may cause partial responses or relapse, with the growth of resistant clones. Besides these, inter-patient heterogeneity, which is variation between tumors of the same type in different patients also complicates prediction models.
2. **Dynamic Immune Microenvironment:** The tumor microenvironment (TME) does not remain stable, but it is modified by the response to therapy and disease progression. The immune cell infiltration (T-cells, NK cells, macrophages), cytokine signals, and checkpoint molecule expression (e.g. PD-L1, CTLA-4) differ by time and between tumor regions. The initially hot (full of immune infiltration) tumor can become cold (immune exclusion) and real-time monitoring becomes necessary but challenging.
3. **Limitations of Biomarkers:** PD-L1 expression and tumor mutational burden (TMB) are the two most commonly used biomarkers at the present to inform immunotherapy. Nonetheless, they are deficient in several aspects: PD-L1 expression may be focal and transient, and TMB is not necessarily associated with immune responsiveness. Other prospective biomarkers, including microsatellite instability (MSI), neoantigen load, and circulating immune signatures are being studied, but none given alone can provide a full forecasting picture.
4. **Mechanisms of Resistance:** Tumors commonly develop resistance mechanisms even at the time of initial response on the part of the patient. These are loss of antigen presentation machinery (e.g. mutations in MHC class I), release of immunosuppressive cytokines and recruitment of regulatory T-cells (Tregs) and myeloid-derived suppressor

cells (MDSCs). The adaptations produce an immunosuppressive niche that mitigates the efficacy of immunotherapy.

Future Directions

- **Multi-omics Approaches:** by integrating genomics, transcriptomics, proteomics, and metabolomics a complete picture on tumor-immune system interaction is provided. In contrast to single-dimensional biomarkers, multi-omics analyses enable biologically layered information and correlate genetic changes, expression changes, protein changes, and metabolic changes. This comprehensive system is able to discover new predictive biomarkers, discover disease pathophysiology, and monitor dynamic alterations in tumor development and immune responses. Finally, it could be possible that multi-omics would allow the use of precision oncology methods as molecular signatures can be associated with therapeutic sensitivity and resistance.
- **Artificial Intelligence (AI) and Machine Learning Models:** AI and machine learning are potent instruments to handle complexity and volume of clinical, pathological, and molecular data. The AI-based predictive algorithms also can help formulate the correct patient stratification systems by identifying nonlinear and subtle patterns that cannot be seen through the traditional statistical methods. Such models have the potential not only to predict responses to treatment, track disease progression, and provide adaptive therapeutic responses in real time, but also to forecast them. Moreover, AI has potential to improve the discovery of biomarkers, clinical trial design, and clinical decision making to drive therapy personalization.
- **Combination Therapies:** Although immune checkpoint inhibitors have been successful in treating patients, resistance or diminished responses are common in many patients, underscoring the need to implement combinatorial approaches. Combination of immune checkpoint blockade with targeted therapy, chemotherapy, radiation therapy, or new immunomodulators will be applied synergistically to recondition tumor microenvironment (TME), stimulate immune activation and evade adaptive resistance mechanisms. Such methods are effective not only in increasing the number of responders, but they also enhance clinical benefit durability. Mechanism-driven and biomarker-driven rational design of combination regimens is an avenue with potential to promote immuno-oncology.

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