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Using Personalized Immunotherapies to Advance Melanoma Treatment

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ABSTRACT

Melanoma, a potentially fatal type of skin cancer, presents as a prominent challenge in oncology, due to its significant mortality rates and aggressive nature. This emphasizes the immediate demand for new, effective treatments which address these obstacles, prompting additional research and a concerted effort to quickly find better treatment options. Personalized immunotherapy, which involves tailoring treatments to the unique characteristics of each patient, offers a promising solution. The integration of personalized immunotherapy into treatments both addresses the complexity of the cancer and enhances the effectiveness of therapies. This review underscores how utilizing personalized immunotherapy alongside immune checkpoint inhibitors, oncolytic viruses, and tumor-infiltrating lymphocyte therapy can significantly improve patient outcomes by effectively targeting and eliminating malignant melanoma tumors.

Introduction

Melanoma, a highly aggressive form of skin cancer, poses a formidable challenge in oncology. The disease is Characterized by its rapid progression and substantial mortality rates, melanoma contributes to a staggering 75% of skin cancer-related deaths in the United States (Brady, et al., 2021). It is notorious for its propensity to metastasize rapidly, spreading to distant organs and tissues throughout the body. This aggressive behavior significantly complicates treatment and diminishes patient prognosis.

Melanoma originates from the uncontrolled growth of melanocytes, the pigment-producing cells located in the epidermis. The development of melanoma typically begins with genetic mutations occurring in these melanocytes, which disrupt the normal regulatory mechanisms governing cell growth and proliferation (Rotte, et al., 2016). These mutations can arise spontaneously or as a result of prolonged exposure to environmental factors, such as ultraviolet (UV) radiation from sunlight. Intense UV exposure can damage the DNA within melanocytes, leading to the accumulation of mutations promoting malignant transformation (Abdel-Malek, et al., 2010). Individuals with certain genetic predispositions, such as mutations in the BRAF or NRAS genes, which encode proteins involved in important cell signaling pathways, are also at increased risk of developing melanoma. Once initiated, malignant melanocytes undergo uncontrolled proliferation, forming a tumor mass that may invade surrounding tissues and eventually metastasize to distant organs (Rotte, et al., 2016).

Due to the aggressive nature of melanoma, it exhibits a significant resistance to conventional treatment options, including chemotherapy and radiation, further complicating its clinical management (Paulson, et al., 2020). Chemotherapy is limited due to melanoma's robust mechanisms for drug resistance, and radiation therapy is not optimal due to the inherent resistance of tumors and the potential for damage to surrounding healthy tissues. Its lethality is intensified by its ability to affect all ages, with a peak incidence observed in older populations (Kuryk, et al., 2020). Melanoma's high propensity for recurrence and the potential for secondary cancers to generate also pose ongoing challenges in long-term disease management (Merlino, et al., 2016). Due to these challenges, personalized immunotherapy has emerged as a promising option for melanoma treatment, as it may

maximize the efficacy and safety of immune checkpoint inhibitors, oncolytic viruses, and tumor-infiltrating lymphocyte therapy.

Personalized Immunology

Personalized immunology is an approach to cancer treatment that tailors therapies to the individual characteristics of each patient (Figure 1). In contrast to conventional immunotherapy approaches, often employing standardized treatments with limited consideration for individual variability, personalized immunology may offer a superior level of precision and efficacy by customizing treatments based on the unique immunological makeup of each patient (Mandal, et al., 2016). Taking these personalized factors into account, such as the patient's overall health and tumor characteristics, also optimizes the safety and efficacy of the treatment (Delhalle, et al., 2018). For example, a patient with melanoma may undergo personalized immunotherapy specifically designed to target the unique mutations present in their tumor cells, while minimizing potential side effects based on their overall health profile. This holds immense potential for improving patient outcomes and advancing cancer treatments (Tarhini, et al., 2018).

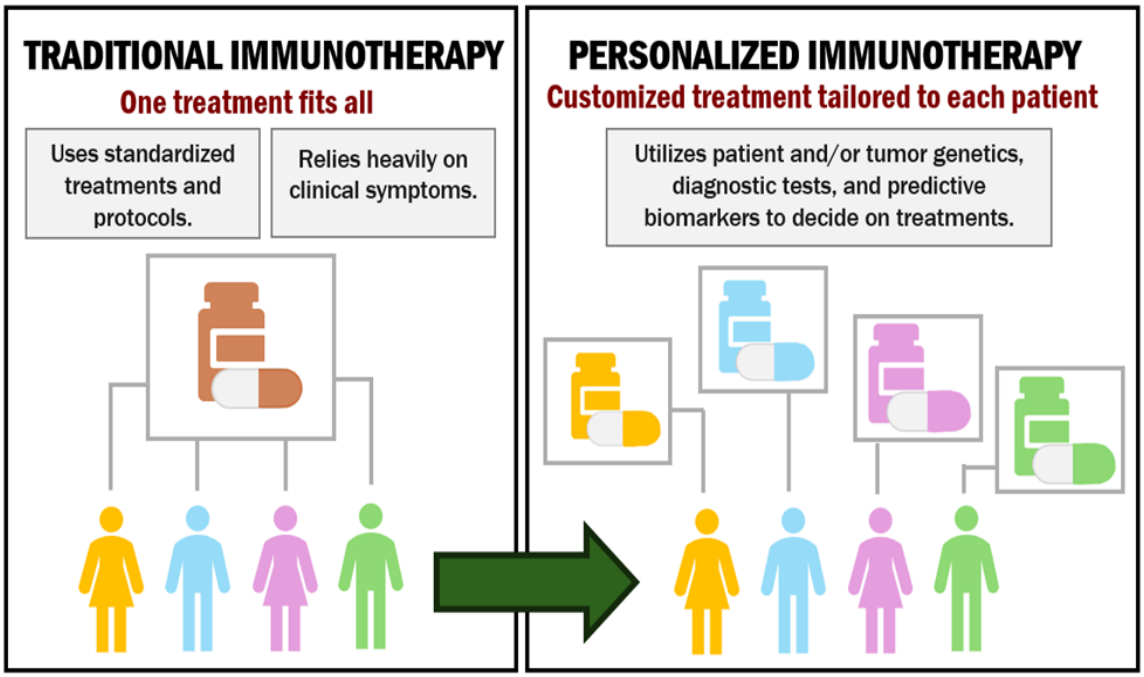

Figure 1. Key differences between traditional immunotherapy and personalized immunotherapy. Traditional immunotherapy uses a set treatment option for many individuals, while personalized immunotherapy looks at certain characteristics of each patient to derive a treatment specific to them.

Immune Checkpoint Inhibitors (ICIs) are a Class of Drugs Designed to Enhance the Immune Response Against Cancer Cells

Within the immune system, pathways known as immune checkpoints play a crucial role in regulating immune responses to maintain homeostasis. These checkpoints regulate the immune system, preventing it from overreacting and causing damage to healthy tissues. This mechanism, however, is exploited by cancer cells to evade

detection, allowing them to proliferate unchecked. ICIs disrupt these immune checkpoints, essentially releasing the brakes on the immune system and allowing it to unleash its full potential in destroying cancer cells.

Personalized ICI therapy involves identifying predictive biomarkers, which can indicate the likelihood of response to treatment. In melanoma treatment, patients with higher levels of programmed death ligand 1 (PD-L1) expression may have better response rates to PD-1 checkpoint inhibitors, making nivolumab and pembrolizumab an optimal choice for treatment (Nakajima, et al., 2021). Additionally, the tumor mutational burden (TMB), which reflects the number of mutations within a tumor, is also a key biomarker for predicting responses due to immune checkpoint inhibitors. Patients possessing tumors with a higher TMB are more likely to produce neoantigens, which can trigger an immune response and enhance the efficacy of this therapy (Sankar, et al., 2022).

Ipilimumab

Ipilimumab is a monoclonal antibody centered on the targeted blockade of CTLA-4, a crucial regulator of T-cell activation. T-cells recognize threats to the body, such as pathogens or cancerous cells, through T-cell receptors (TCRs). These receptors are uniquely shaped, in order to bind with specific antigenic peptides, present on infected cells. Once threats are recognized by TCRs, protein CD28 provides and amplifies signals to activate T cells (Lee, et al., 2016).

CD28 interacts with ligands CD80 and CD86 to amplify these signals. CTLA-4, found on the surface of T-cells, regulates protein CD28 by also interacting with these molecules. CTLA-4 overpowers the effect of CD28, reducing its ability to bind with the ligands, and controls T-cell activation, especially during their responses to infections or cancer (Bagchi, et al., 2021).

Ipilimumab intervenes early in the process of T-cell activation by selectively inhibiting CTLA-4. By doing so, it facilitates sustained T-cell activation and proliferation, increasing the immune system's ability to eliminate malignant cells, and strengthening the efficacy of the body's immune response (Mansh, 2011).

Clinical validating of ipilimumab's efficacy was demonstrated in a phase III study, where patients with pretreated advanced melanoma were randomly assigned to receive ipilimumab alone, a gp100 vaccine alone, or a combination of the two. Patients were administered four consecutive doses of 3 mg/kg every three weeks, leading to greatly improved overall survival (OS). Pure ipilimumab resulted in an average of 10 months OS, while the gp100 vaccine resulted in 6.4 months (Rogiers, et al., 2019). The combination of both had no significant increase in OS, emphasizing ipilimumab's impact on prolonging survival for patients with melanoma and leading to its approval for clinical use in March 2011 (Robert, et al., 2013).

Nivolumab and Pembrolizumab

Nivolumab and pembrolizumab are monoclonal antibodies belonging to a class of drugs known as PD-1 inhibitors. PD-1 is a protein found on the surface of T-cells, playing a pivotal role in regulating T-cell activity during inflammatory responses (Lee, et al., 2016). PD-1 interacts with its ligands PD-L1 and PD-L2, providing a signal which effectively suppresses its function, in order to prevent excessive immune responses and maintain immune homeostasis. This mechanism is normally exploited by cancer cells to evade the immune system, promoting tumor growth and progression (Martin-Liberal, et al., 2015).

Both nivolumab and pembrolizumab bind to the PD-1 receptor, preventing PD-1 to interact with its ligands. By blocking the PD-1 pathway, the immune system is able to work at its full potential, allowing T-cells to remain active and functional. This enhances its ability to recognize and attack cancer cells, which would otherwise evade detection (Khoja, et al., 2015).

The efficacy of nivolumab and pembrolizumab in enhancing the immune response against melanoma has been established through many clinical studies. One such study was a phase I study, where patients above

18 years of age with advanced melanoma were divided and received pembrolizumab at different doses and frequencies (Hamid, et al., 2019). The study included 655 melanoma patients, with an average monitoring time of 55 months, receiving treatment until the cancer continued to worsen or there was a decision to stop. The estimated 5-year OS time was 34% for all patients, with a median OS of 23.8 months, signifying a considerable delay in disease progression, and leading to its approval for clinical use (Hamid, et al., 2019).

Studies conducted have suggested that there is no significant difference between nivolumab and pembrolizumab. A study utilizing data from Flatiron Health Database compared the two treatment options in patients with advanced melanoma, diagnosed between January 2011 and July 2018 (Moser, et al., 2020). From the final data, 486 received pembrolizumab and 402 received nivolumab, resulting in a median OS of 22.6 months for all patients, with no drastic difference shown. Both treatments, however, did improve the patients outcome overall, increasing their OS and reducing the progression of the cancer (Moser, et al., 2020). This equivalence in efficacy provides flexibility in treatment options based on other factors like side effects, patient preference, or availability.

Challenges Regarding ICIs

While ICIs can unleash the immune system's ability to target melanoma cells, they may also lead to immune-related adverse events (irAEs), which can develop into autoimmune reactions due to the heightened activity of the immune system. These irAEs can affect various organs and systems in the body, ranging from mild to severe symptoms, and may require prompt intervention with immunosuppressive agents to manage effectively (De Miguel, et al., 2020). Examples of irAEs include dermatologic reactions like rashes, gastrointestinal issues such as colitis and hepatitis, endocrine disorders including hypothyroidism or hyperthyroidism, pulmonary issues, and cardiovascular effects. Additionally, not all patients respond to ICIs, primarily due to factors such as tumor heterogeneity and individual differences in the immune system. This variability poses a considerable obstacle in predicting and optimizing treatment outcomes, requiring other approaches to therapy (Dobosz, et al., 2022).

Oncolytic Viruses (OVs) are Engineered Viruses Which Selectively Target and Infect Cancer Cells

OVs exploit the weaknesses inherent in tumors, while sparing healthy cells, holding immense potential for improving melanoma treatment and reducing its side effects (Lawler, et al., 2017). Selective replication within tumor cells is one of the key strategies employed by OVs. Through genetic modifications, these viruses contain genetic sequences that are activated only around tumor-specific igniting pathways, meaning they are designed to replicate preferentially within only tumor tissues (Everts, et al., 2005). From here, OVs multiply, causing targeted cancer cells to rupture, and neighboring cancer cells to become infected due to the release of newly formed virus particles. This process of viral infection and cancer cell lysis releases tumor antigens, recognizable by the immune system, leading to a stimulated immune response against cancer cells, in addition to the targeted attack provided by OVs. This approach has been proven successful against melanoma, as it can exploit the overexpression of specific receptors present in melanoma cells and infect them, rather than affecting the healthy ones as well (Lawler, et al., 2017).

In personalized immunotherapy, OVs can be customized for each patient through various methods to enhance treatment efficacy. This treatment option is favorable for patients who exhibit a favorable tumor microenvironment characterized by high levels of immune cell infiltration, expression of immunogenic antigens, and low immunosuppressive factors (Stavrakaki, et al., 2021). In terms of melanoma, OVs can be engineered to exploit genetic alterations, such as mutations in the BRAF and NRAS genes. Patients who have failed prior treatments, such as chemotherapy or targeted therapy, may benefit from oncolytic virus therapy as a salvage treatment option as well (Fukuhara, et al., 2016).

Talimogene Laherparepvec (T-VEC)

In 2015, T-VEC became the first oncolytic virus to gain FDA approval in the United States. It is derived from herpes simplex virus type 1 (HSV-1), but is modified to remove gene ICP34.5, which is required for replication in nerve cells and can cause nerve damage (Johnson, et al., 2015). T-VEC is injected into the tumor, then infects and destroys cancer cells, while also inducing immune responses targeting cancer cells in other parts of the body (Marelli, et al., 2018).

In a phase II study involving 50 patients afflicted with advanced melanoma, treatment with T-VEC every three weeks yielded notable successful outcomes, with 26% of patients exhibiting a positive response to the therapy. Out of these responses, 12 had lasting effects persisting for over six months, and 8 out of 13 individuals achieved complete responses, including a significant antitumor effect (Johnson, et al., 2015). These findings emphasize the potential of T-VEC as a viable treatment option for patients with melanoma, providing promising results for improving patient outcomes.

The success of T-VEC is also significant when comparing it to other treatment options. A randomized phase III study, comparing T-VEC to GM-CSF, a protein enhancing the immune system's ability to recognize and attack tumor cells, shows that T-VEC has a higher durable response rate of 16.3%, compared to the 2.1% from GM-CSF (Ferrucci, et al., 2021). This significant difference underscores the effectiveness of T-VEC against melanoma, highlighting its potential as a treatment option.

Coxsackievirus A21 (CVA21)

CVA21 is an enterovirus which interacts with specific cell receptors, ICAM-1 and DAF, to stimulate an immune response against melanoma. ICAM-1, the primary receptor for viral attachment, and DAF, the secondary receptor, are both adhesion molecules typically overexpressed on cancer cells. CVA21 targets cells with high levels of these molecules, which explains its ability to selectively target malignant cells (Au, et al., 2005). Once inside the target cells, the virus goes through oncolysis, the process of virus replication and the subsequent lysis of the infected cancer cells, and eventually dies off (Bradley, et al., 2014).

A phase II study investigated the effectiveness and safety of CVA21 for patients with advanced melanoma. In this study, 54 patients with advanced melanoma were injected with CVA2, of which 38.6% of them experienced immune related progression-free survival (irPFS) at six months of treatment (Andtbacka, et al., 2015). The majority of adverse events were classified as Grade 1, such as fatigue, chills, and fever. The study concluded that the injection of CVA21 is a promising treatment for advanced melanoma, drastically improving outcomes for patients (Bradley, et al., 2014). To personalize treatment, the study measured clinical parameters such as tumor response and adverse events, demographic factors like age and gender, and lifestyle aspects including patients' overall health and any concurrent treatments. This comprehensive approach helps tailor the treatment to individual patient profiles, enhancing its effectiveness and safety.

Adenovirus

Adenovirus is a virus belonging to the Adenoviridae family, typically interacting with the coxsackie and adenovirus receptor (CAR) on the surface of cancer cells to infect them. CAR serves as the primary receptor for the attachment of adenoviruses to the cell membrane, however in regards to melanoma, they may interact with other receptors that are typically overexpressed or uniquely present on cancer cells as well (Mantwill, et al., 2021). After attachment to receptors, adenoviruses are internalized into melanoma cells through endocytosis, a process where extracellular molecules or particles are engulfed by the cell membrane and incorporated into endosomes. The viral DNA is released into the cytoplasm, where after transcription, newly synthesized viral proteins form

mature adenovirus particles within the nucleus of the cancer cell. From here, adenoviruses continue replicating and eventually destroy the cancer cells (McCart, et al., 2002).

Challenges Regarding Oncolytic Viruses

While the immune system's recognition and elimination of viruses are essential for therapeutic efficacy, pre-existing immunity or the rapid development of neutralizing antibodies can hinder the ability of OVs to reach and infect tumor cells. The immune response directed against the virus may also limit its replication and spread within the tumor microenvironment, thereby attenuating its anti-tumor effects. Factors such as tumor hypoxia, which occurs when tumors lack oxygen, can impede viral spread and effective tumor targeting as well (Aurelian, 2016). Another challenge is the potential for off-target effects and systemic toxicity associated with this therapy. Mitigating these requires the careful design and engineering of OVs to minimize harm to normal tissues (Lauer, et al., 2022).

Tumor-Infiltrating Lymphocyte (TIL) Therapy is an Adoptive Cell Therapy Representing a Promising Approach to Melanoma Treatment

TIL therapy harnesses the power of TILs, immune cells that naturally infiltrate the tumor microenvironment, highlighting their potential to recognize and attack cancer cells. A portion of the patient's tumor is surgically removed and processed to isolate TILs (Feldman, et al., 2015). These are then cultured in a laboratory, typically through exposure to specific growth factors such as Interleukin-2, which promote their proliferation. Prior to infusion, lymphodepletion therapy is administrated, temporarily suppressing the patient's immune system with chemotherapy drugs, creating space within the body for the infused TILs to function properly. The activated TILs are then injected into the patient, with the goal of targeting and destroying cancer cells, including both the primary tumor and any metastatic lesions (Figure 2) (Merhavi-Shoham, et al., 2017).

Upon infusion into the patient, the activated TILs employ various mechanisms to attack tumor cells, such as direct cell killing, a process in which cytotoxic T-lymphocytes (CTLs), among the infused TILs, directly engage with and attack cancer cells. This process involves the release of cytotoxic molecules, such as perforin and granzymes, which trigger apoptosis in the cancer cells (Kumar, et al., 2021). TILs can also induce indirect cell killing through the release of cytokines, such as interleukins, which also have the ability to induce apoptosis in cancer cells. This dual mechanism of action allows TILs to effectively target and eliminate tumor cells (Geukes Foppen, et al., 2015).

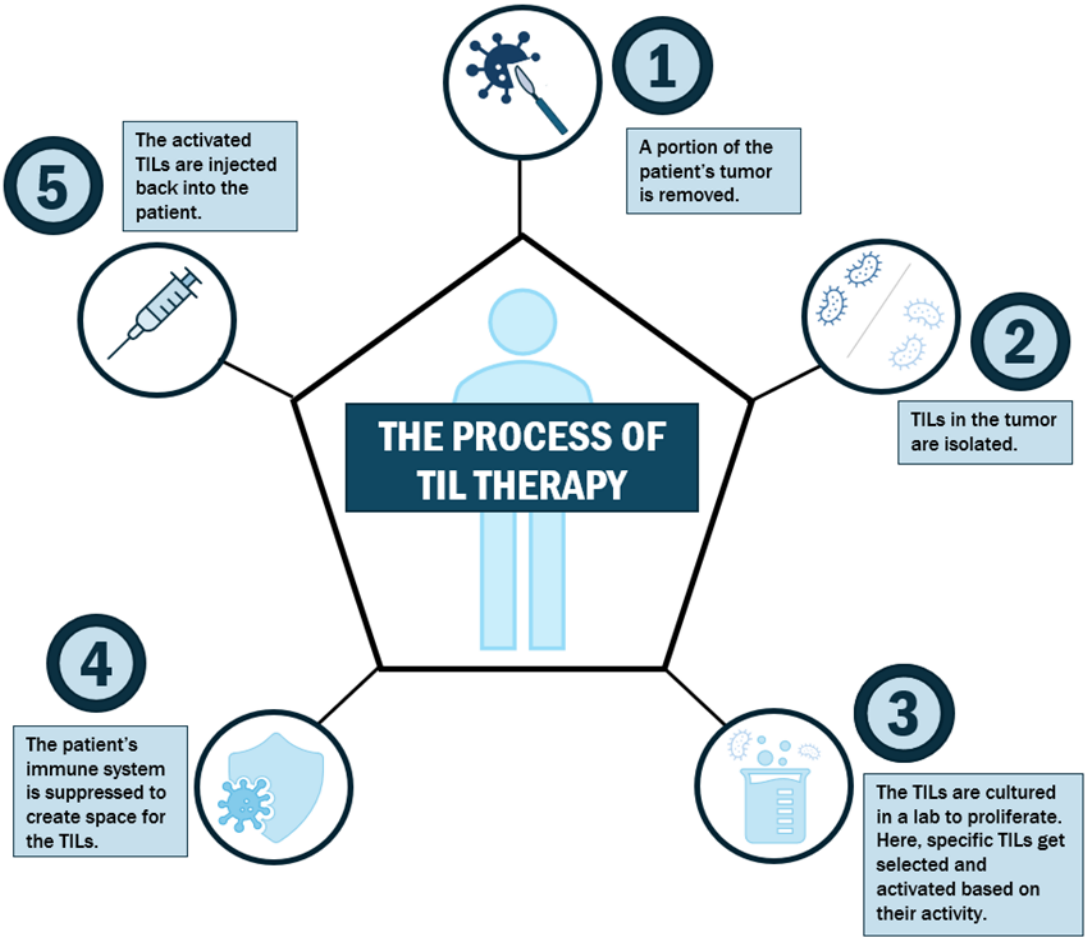

Figure 2. The process of TIL therapy. This includes the steps involved in isolating, culturing, and infusing activated TILs into patients for targeted melanoma treatment.

A study investigating the efficacy of TILs for metastatic melanoma treatment yielded extremely promising results. Conducted on a cohort of 10 patients, all aged at least 18 years old, the study revealed that half of the patients experienced an objective clinical response to the treatment. Notably, two patients achieved a complete response, indicating the complete disappearance of their tumors, and have endured these results for more than seven years (Hong, et al., 2010). A key finding in this study was that the TILs utilized in the treatment demonstrated the ability to target specific mutations in the tumor cells, leading to tumor regression and long-term remission in treated patients, underscoring the promising potential of TIL therapy as a treatment option for melanoma (Hall, et al., 2023). These results suggest that TIL therapy is especially beneficial for adult patients with melanoma, particularly those whose tumors exhibit targetable mutations.

Success rates in melanoma treatment with TIL therapy vary based on patient-specific factors. In this case, younger patients, typically with lower tumor burdens, tend to have higher success rates with TIL therapy (Goff, et al., 2010). Tumors with high immunogenicity, meaning they elicit an immune response and demonstrate minimal immune suppression, show enhanced susceptibility to this treatment. These types of tumors often produce neoantigens, antigens that arise from tumor-specific mutations, which are highly recognizable by TILs, leading to the cell's destruction (Antohe, et al., 2019).

Challenges Regarding Tumor-Infiltrating Lymphocyte Therapy

TIL therapy also faces several challenges that must be addressed to optimize its efficacy and clinical application. A major challenge is the limited availability of suitable TILs for therapy. Obtaining a sufficient number from patient tumor samples can be challenging, particularly in cases where tumors are small or have low levels of immune infiltration (Zablocka, et al., 2021). TIL therapy can also be associated with significant toxicity and adverse events, including cytokine release syndrome (CRS) and neurotoxicity. These can lead to fever, hypotension, and organ dysfunction, requiring immediate management to mitigate further complications (Zhao, et al., 2022).

Conclusion

The challenges associated with melanoma have been significantly addressed through personalized immunotherapy, which offers tailored treatments to combat the cancer's aggressive nature and resistance to traditional therapies. Personalized immune checkpoint inhibitors, oncolytic viruses, and tumor-infiltrating lymphocyte therapy show promise in selectively targeting and eliminating tumor cells effectively, despite challenges such as immune-related side effects and varying patient responses. As research on this topic continues to develop, the emergence of personalized neoantigen-loaded nanoparticles holds potential as a promising direction for further experimentation, as they enhance treatment success while minimizing adverse effects. This progress signifies a pivotal advancement in melanoma treatment, indicating a transition towards more refined and individualized therapeutic strategies using personalized immunotherapy.

Future Directions

A promising direction for advancing melanoma treatment lies in the development of personalized neoantigen-loaded nanoparticles. This approach involves using nanoparticles to deliver vaccines designed from patient-specific neoantigens, which by leveraging genomic sequencing, can be uniquely identified and synthesized into peptides, forming the basis of a personalized vaccine. In the future, these vaccines could be encapsulated in biocompatible nanoparticles, which are then functionalized with ligands to target melanoma-specific markers, ensuring precise delivery to the tumor site (Chu, et al., 2018). This method offers the potential for high specificity and potency, while minimizing off-target effects and reducing toxicity as well. It also holds promise for use with existing treatments, such as ICIs, and may increase the efficacy of these existing treatments. Future research could focus on developing advanced biomarkers to better predict patient response and creating adaptive nanoparticles that respond to changes in the tumor environment (Reynolds, et al., 2022). This research will also assist in overcoming the challenges associated with personalized immunotherapies, as understanding these factors improves the precision and effectiveness of these treatments. This innovative idea represents a significant leap forward in personalized immunology for melanoma treatments, offering the potential to greatly enhance therapeutic outcomes and improve patient survival rates.

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