Recent advances in immunotherapy in cancer treatment

Ayyub A. Patel

Department of Clinical Biochemistry, College of Medicine, King Khalid University Abha, Kingdom of Saudi Arabia

Abstract

Immunotherapy has emerged as a transformative approach in cancer treatment, leveraging the body’s immune system to recognize and eradicate cancer cells. This review provides an overview of the recent advances and aspects of immunotherapy in cancer biology, from established therapies like checkpoint inhibitors and CAR-T cells to emerging innovative approaches and the challenges associated with their clinical translation. The exploration includes an examination of checkpoint inhibitors, elucidating the mechanisms behind programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors. Recent clinical successes and ongoing trials demonstrate the efficacy of checkpoint inhibitors across diverse malignancies, underscoring the potential for durable responses and improved patient outcomes. CAR-T cell therapy represents a groundbreaking avenue in immunotherapy, involving the genetic modification of a patient’s T cells to express chimeric antigen receptors (CARs) for targeted cancer cell recognition. Furthermore, the review touches on the challenges associated with immunotherapy, including resistance mechanisms and adverse effects. Insightful discussions on overcoming resistance through combination therapies, adaptive treatment strategies, and emerging technologies underscore the ongoing efforts to enhance the long-term efficacy of immunotherapeutic interventions. In summary, this extensive review provides a comprehensive overview of recent advances in immunotherapy in cancer biology, highlighting the transformative impact of these therapies on patient outcomes, the challenges faced, and the promising directions for future research and clinical applications.

Keywords: Cancer therapy; Checkpoint inhibitors; Biomarkers; CAR-T cells; Cancer vaccines; Immune system

1. Introduction

Cancer is one of the most complicated and deadly diseases affecting the health of human. A number of genes and factors are involved in it [1]. There are several forms of cancer affecting almost every vital and not vital part of the body including stomach, cervix, breast, lung, throat, blood, and skin [2, 3]. It is a multifaceted disease and a multifaceted approach is essential to combat it [4]. One of the targeted therapies include the use of RNAs (long non-coding RNAs and microRNA) which have showed effective contribution in eliminating tumors owing to their role in many cellular processes and chemical reactions inside the human body [5] [6]. They can be effective biomarkers in targeted cancer therapy as biomarkers are quite helpful in the diagnosis of cancer and its early treatment [7]. CDH1 and DCC genes which are silenced by hypermethylation in gastric cancer, their bioinformatics analysis at the genome and proteome level and evaluation show that these tumor suppressor genes can be utilized for targeted treatments in cancer [8]. Further, metal and metal-based nanoparticles have shown progress in increasing anticancer mechanism [9]. But, due to the unwanted side effects of such metal based and other synthetic compounds based cancer therapy, research is more focused on harnessing anticancer agents from the natural products (plants, marine and microorganisms) [10]. One study explored interaction of α-pinene, a plant product, with testis-specific protein on Y chromosome (TSPY), whose expression has been observed in gonadoblastoma and carcinoma [11]. Based on in silicomolecular docking analysis, this interaction can be helpful in developing α-pinene as a promising candidate for the new anticancer agent.

Immunotherapy has emerged as a revolutionary approach in cancer therapy, representing a paradigm shift in the treatment of various malignancies [12, 13]. Unlike traditional treatments such as chemotherapy and radiation that directly target cancer cells, immunotherapy harnesses the body’s immune system to recognize and combat cancer by selectively attacking cancer cells, often sparing normal cells from the collateral damage associated with traditional treatments [14]. This approach has demonstrated the potential for prolonged and durable responses in some patients. Unlike conventional therapies that may require continuous treatment, immunotherapy such as checkpoint inhibitors and adoptive cell therapies, has shown the ability to induce long-lasting remissions and also cures, in
some cases.

Most of the cancer types have been life-threatening and greatest challenges in the medical field. Immunotherapy has shown efficacy in cancers that were historically challenging to treat, including some metastatic or advanced-stage cancers [15]. This has expanded treatment options for patients with limited alternatives and poor prognoses. It also often results in fewer side effects compared to traditional treatments like chemotherapy. As it heightens the body’s immune system, the adverse effects are typically related to immune activation and are generally milder than the toxicities related to traditional therapies. Moreover, immunotherapy can be combined with other treatment modalities, including chemotherapy, radiation, and targeted therapies, to enhance overall treatment efficacy. This synergistic approach has the potential to overcome resistance mechanisms and improve outcomes.

In the realm of cancer vaccines and adoptive cell therapies, advances in immunotherapy can contribute to the growing field of personalized medicines. Tailoring treatments based on individual patient profiles, including immune system status and tumor characteristics, allows for more effective and precise interventions. One of the several benefits that immunotherapy offers, is that it has the unique advantage of potentially inducing immunological memory [16]. It means that even after treatment is completed, the immune system may “memorize” and recognize cancer cells, providing ongoing protection against recurrence. The approval of various immunotherapies across different cancer types has expanded the treatment landscape [17]. Immunotherapy is now a standard of care for certain cancers and ongoing research continues to explore its potential in additional malignancies. The success of immunotherapy has sparked considerable research and innovation in the field. Ongoing studies aim to refine existing therapies, discover new targets, and develop novel approaches, fostering a dynamic and rapidly evolving landscape in cancer treatment.

2. Brief historical context of cancer immunotherapy

The roots of cancer immunotherapy can be traced back to the late 19th century. Even before that, in the late 1800s, William Coley, a surgeon, observed that some cancer patients experienced spontaneous remission after bacterial infections [18]. He began injecting cancer patients with a mixture of heat-killed bacteria, known as Coley’s toxins. Although the mechanisms were not well understood at that time, this marked an early attempt at stimulating the immune system to attack cancer. Later, scientists identified tumor-specific antigens, substances unique to cancer cells, in the 1950s and 1960s [19]. This laid the groundwork for developing strategies to target these antigens, aiming to trigger an immune response against cancer. In the 1970s, researchers began to uncover the role of lymphocytes, particularly T cells, in recognizing and attacking cancer cells [20]. T cells play a crucial role in the immune system, responsible for recognizing and attacking abnormal cells [21]. This period marked a shift in understanding the importance of the cellular immune response in cancer surveillance. The development of monoclonal antibodies in the late 20th century marked the targeted recognition of specific antigens on cancer cells [22]. Rituximab, the first monoclonal antibody approved for cancer treatment [23], became a landmark in immunotherapy by targeting B-cell lymphomas [24]. Tremelimumab, another monoclonal antibody targeting CTLA-4 underwent clinical evaluation. However, it was dosed less frequently due to its longer half-life [25].

Interleukin-2, a cytokine involved in immune cell activation, gained attention in the 1980s for its potential to enhance the body’s immune response against cancer [26]. High does IL-2 was one of the first immunotherapies to demonstrate efficacy [27], leading to its approval for metastatic melanoma and renal cell carcinoma [28]. It was the identification of immune checkpoint molecules, such as CTLA-4 [29] and PD-1 [30], in the 1990s and early 2000s, that paved the way for the development of checkpoint inhibitors. Blocking both PD-1 and CTLA-4 in combination enhanced the infiltration of effector T-cells into B16 melanoma in mice. This led to an increased ratio of effector to regulatory T-cells within the tumor [31]. Ipilimumab, the first CTLS-4 inhibitor, was improved in 2011 for metastatic melanoma [32], marking a breakthrough in unleashing the immune system against cancer.

Chimeric Antigen Receptor T-cell (CAR-T) therapy emerged as a revolutionary approach. In the 2010s, CAR-T therapies like Kymriah and Yescarta were approved for certain types of leukemia and lymphoma [33], showcasing the power of genetically engineered T-cells in targeting cancer. Cancer immunotherapy’s groundbreaking researches were recognized with Nobel Prizes when James Allison and Tasuku Honjo were awarded the Nobel prize in physiology in 2018 for their contributions to immune checkpoint inhibitions [34]. The field of cancer immunotherapy continues to advance rapidly with ongoing research focusing on combination therapies, personalized vaccines, and innovative approaches. The development of new immunotherapies and the expansion of indications for existing ones underscore the dynamic nature of the field.

3. Immune checkpoint inhibitors

The immune system plays a critical role in surveillance and elimination of aberrant cells, including cancer cells. Immune checkpoint is a kind of signal (stimulatory or inhibitory) for regulating the antigen recognition of T cell receptors in the process of immune response of attacking pathogens and protecting the normal tissues from damage. However, cancer cells can exploit these regulatory mechanisms to evade immune detection and destruction. Immune checkpoint proteins play a significant role in cancer evasion [35]. These molecules are expressed on the surface of immune cells that regulate the intensity and duration of immune responses. They serve as ‘brakes’ to prevent over-activation of the immune system and maintain self-tolerance [36]. Cancer cells often upregulate the expression of checkpoint proteins or their ligands as a mechanism of immune evasion. By engaging these proteins, cancer cells can suppress T cell activity, avoid immune detection, and establish an immunosuppressive microenvironment. This evasion strategy allows cancer cells to proliferate and resist immune-mediated elimination. Therapy based on these checkpoint proteins relies on functioning immune system with agonists of stimulatory signals or antagonists of inhibitory signals. Table 1 represents several immune checkpoint proteins that play crucial roles in regulating the immune response. Immune checkpoint inhibitors (Figure 1), negative regulators of the immune system, are key regulators in maintaining immune homeostasis and pre-
vent preventing excessive immune responses [37, 38]. Common checkpoint proteins include programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).

PD-1 is expressed on the surface of T-cells, while PD-L1 is often upregulated on the surface of cancer cells and other immune cells with in the tumor microenvironment. When PD-1 on T-cells binds to PD-L1 in cancer cells, it leads to a suppression of T-cell activity. This interaction inhibits the immune system’s ability to recognize and eliminate cancer cells, allowing them to evade surveillance [39]. PD-1 inhibitors, such as pembrolizumab and nivolumab, block this interaction, preventing the suppression of T-cell responses [40]. PD-1 inhibitors have received FDA approval for various cancer types including melanoma, non-small cell lung cancer (NSCLC) [41], and renal cell carcinoma. These drugs have demonstrated durable responses and improved survival rates in a subset of patients. On the other hand, PD-L1 inhibitors, such as atezolizumab and durvalumab, directly target the ligand expressed in cancer cells [42]. By inhibiting the PD-1/PD-L1 interaction, these drugs enhance T-cell activity and promote anti-tumor immune responses. Recent assessments in humans, marking the first use of PD-L1 imaging agents, have introduced non-invasive, molecularly targeted quantitative measures. These measures aim to guide and evaluate the immune response to immune checkpoint therapy [43]. Furthermore, the expression of PD-L1 on tumor cells is often used as a biomarker to predict responsiveness to these inhibitors which have shown efficacy in various cancers, including bladder cancer, triple-negative breast cancer, and NSCLC [44, 45].

CTLA-4 is another checkpoint protein expressed in T cells. It competes with the co-stimulatory molecules CD28 for binding to B7 ligands on antigen-presenting cells (APCs) [46]. Thus, CTLA-4 inhibits T-cell activation and dampens the immune response [47]. Cancer cells can exploit this pathway to evade immune detection by downregulating co-stimulatory signals necessary for effective T cell activation. CTLA-4 inhibitors, such as ipilimumab, block CTLA-4 leading to enhanced T-cell activation and proliferation [48]. These inhibitors have demonstrated efficacy in metastatic melanoma. Ipilimumab was the first immune checkpoint inhibitor to receive FDA approval in 2011. The combination of CTLA-4 and PD-1 inhibitors has further improved outcomes in melanoma and other malignancies [49], but not without the increased incidence of adverse effects.

However, not all patients respond to checkpoint inhibitors and resistance mechanisms can develop. Immune-related adverse events, although generally manageable, can occur and require vigilant monitoring. Identification of predictive biomarkers, such as microsatellite instability (MSI), PD-L1 expression on tumor cells and tumor mutational burden (TMB), has become crucial for selecting patients who are likely to respond to checkpoint inhibitors [50, 51]. This has paved the way for personalized medicine in the field of immunotherapy. Thus, despite the success of checkpoint inhibitors, challenges such as resistance mechanisms and immune-related adverse events persist. Ongoing research aims to unravel the complexities of the tumor microenvironment, identify additional checkpoint pathways, and develop novel targets and combination therapies to enhance the efficacy of immunotherapy and overcome resistance.

4. Enhancing the efficacy of checkpoint inhibitors

Antitumor therapies and immune checkpoint inhibitors have proved clinical efficacy for some indications, but are limited by toxicity and resistance development. Several emerging strategies are being explored to optimize the effectiveness of checkpoint inhibitors. One strategy is combination therapies. To maximize the probability of therapeutic success, it is imperative that those strategies must be able to increase tumor immunogenicity, favor intra-tumor T cell trafficking and reduce tumor burden. Combining inhibitors targeting different checkpoint proteins, such as PD-1 and CTLA-4, has shown synergistic effects in clinical trials [49]. The combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) has shown potential treatment for certain cancers, like NSCLC and melanoma [76, 77]. Furthermore, combining checkpoint inhibitors with target therapies such as tyrosine kinase inhibitors [78] such as lenvatinib in combination with pembrolizumab [79, 80] or PARP inhibitors [81, 82], is being explored to address specific vulnerabilities within the tumor microenvironment and enhance the overall antitumor response in advanced breast cancers that are resistant to the conventional therapeutic protocols. However, optimizing combination therapies involves a multifaceted approach. Key considerations encompass the identification of reliable biomarkers for treatment response prediction, vigilant monitoring of responses and side effects, precise patient stratification based on individual characteristics, understanding potential drug interactions, anticipating and addressing resistance mechanisms, ensuring patient adherence, determining optimal timing for treatment components, embracing personalized medicine, considering immunogenicity, and evaluating potential long-term effects. By addressing these aspects comprehensively, the development and implementation of combination therapies can be refined to enhance efficacy and patient outcomes.

Another approach is engineering bispecific antibodies to simultaneously target two different antigens [83-85]. These antibodies can engage both a checkpoint protein and a tumor-specific antigen, further activating T cells and enhancing their cytotoxic activity [86]. Such method has the
### Table 1. Immune checkpoint proteins in the regulation of the immune response.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Immune checkpoint proteins</th>
<th>Expression on</th>
<th>Mechanism of action</th>
<th>Immune checkpoint inhibitors</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>PD-1</td>
<td>Surface of T cells</td>
<td>Binds to PD-L1 causing suppression of T-cell activity</td>
<td>Nivolumab, Pembrolizumab, and Cemiplimab</td>
<td>[39] [40]</td>
</tr>
<tr>
<td>2.</td>
<td>PD-L1</td>
<td>on the surface of cancer cells and other immune cells with in the tumor microenvironment</td>
<td></td>
<td>Atezolimumab, Durvalumab and Avelumab</td>
<td>[42]</td>
</tr>
<tr>
<td>3.</td>
<td>CTLA-4</td>
<td>T cells</td>
<td>Binds to B7 ligands on APCs, inhibiting T cell activation</td>
<td>Ipilimumab</td>
<td>[48]</td>
</tr>
<tr>
<td>4.</td>
<td>Lymphocyte activation gene 3 (LAG-3)</td>
<td>Activated T cells and regulatory T cells</td>
<td>Binds to MHC-II molecules on APCs, inhibiting T-cell activation</td>
<td>Small molecule</td>
<td>[52, 53]</td>
</tr>
<tr>
<td>5.</td>
<td>TIM-3</td>
<td>T cells and other immune cells</td>
<td>Interacts with galectin-9 and other ligands, regulating T cell function</td>
<td>Cobolimab, LY3321367, or sabatolimab</td>
<td>[55, 56]</td>
</tr>
<tr>
<td>6.</td>
<td>TIM-3</td>
<td>Myeloid cells and T cells</td>
<td>Inhibits T cell activation, involved in maintaining immune tolerance</td>
<td>CA-170</td>
<td>[58-60]</td>
</tr>
<tr>
<td>7.</td>
<td>T cell immunoreceptor with Ig and ITIM domains (TIGIT)</td>
<td>T cells and natural killer (NK) cells</td>
<td>Binds to CD155 on APCs, inhibiting T cell and NK cell activity</td>
<td>TgMab-2</td>
<td>[62]</td>
</tr>
<tr>
<td>8.</td>
<td>B- and T- lymphocytes attenuator (BTLA)</td>
<td>B cells, T cells and dendritic cells.</td>
<td>Suppresses immune response</td>
<td>Anti-BTLA Antibody</td>
<td>[64, 65]</td>
</tr>
<tr>
<td>9.</td>
<td>CD40/CD40L (CD154)</td>
<td>APCs and activated T cells respectively</td>
<td>Crucial for T cell priming and B cell activation</td>
<td>Small molecules</td>
<td>[66, 67]</td>
</tr>
<tr>
<td>10.</td>
<td>Ox40 (CD134)</td>
<td>Activated T cells</td>
<td>Interacts with Ox40 ligand on APCs, promoting T cell survival and function.</td>
<td>OX40L-Fc fusion proteins</td>
<td>[68, 69]</td>
</tr>
<tr>
<td>11.</td>
<td>Siglec-15</td>
<td>Macrophages and myeloid cells</td>
<td>Involved in immune regulation associated with tumor-associated macrophages</td>
<td>anti-Siglec-15 mAb</td>
<td>[70, 71]</td>
</tr>
<tr>
<td>12.</td>
<td>4-1BB (CD137)</td>
<td>Activated T cells</td>
<td>Interacts with its ligand (4-1BBL) enhancing T cell proliferation and cytokine production</td>
<td>PRS-343</td>
<td>[72, 73]</td>
</tr>
</tbody>
</table>
potential to trigger a more focused immune system activation, resulting in increased effectiveness and minimized peripheral side effects. Bispecific T cell engagers (BiT-cells) are an example of this approach [87]. Additionally, stimulator of interferon genes (STING) activation can enhance the release of pro-inflammatory signals, promoting the recruitment and activation of immune cells within the tumor microenvironment, thus sensitizing tumors to checkpoint inhibition [88, 89]. Recently, a study suggested that paclitaxel, a widely used chemotherapeutic agent in breast cancer, has the capability to produce micronuclei, aligning with the activation of cyclic GMP-AMP synthase-STING in post-mitotic triple-negative breast cancer cells that survive [90]. Additionally, in a cGAS-dependent manner, paclitaxel can also prompt the polarization of macrophages towards an M1 phenotype. This process may play a role in lymphocyte recruitment in certain TNBC samples, potentially contributing to improved patient survival when undergoing combination therapy, though in vivo studies are needed to confirm these findings. Combining cancer vaccines with checkpoint inhibitors can be another strategy which is being explored to induce a more robust and sustained antitumor immune response [91]. Continued studies show that the combination can elevate the antitumor efficacy with safety and toxicity in an acceptable range compared to single-agent vaccine or inhibitors alone [92]. Strategies to improve antigen presentation, such as dendritic cell-based therapies, are also under investigation [93, 94]. Such therapies aim to improve antigen presentation potency to elicit powerful immune responses against tumor cells. The novel approach of combining dendritic cell-based cell therapy with monoclonal antibodies against novel immune checkpoints holds promise to increase the response rate of cancer patients [95].

5. Chimeric antigen receptor T cell (CAR-T) therapy

Cart-T therapy is an innovative form of immunotherapy that harnesses the patient’s immune cells, specifically T cells, to recognize and attack cancer cells [96]. It is a personalized and highly targeted approach that has shown remarkable success, particularly in treating certain types of blood cancers. The CAR typically consists of three main components [97]. The first one is extracellular domain which is responsible for recognizing specific antigens on the surface of cancer cells. It is often derived from an antibody and is designed to target a particular protein expressed in the cancer cell. Second is transmembrane domain that anchors the CAR within the T cell membrane, ensuring stability. The last one intracellular domain which contains signalling domains that activate the T cell upon binding to the cancer cell. Common signalling domains include CD3-zeta and co-stimulatory domains like CD28 or 4-1BB.

The therapy begins with the extraction of T cells from the patient’s body and is genetically modified in the laboratory [98]. The key modification involves introducing a chimeric antigen receptor (CAR) into the T-cells. This CAR is a synthetic receptor that combines components from both the immune system and antibodies. These genetically modified T-cells equipped with CAR, are cultured to multiply these CAR-T-cells and activate T-cells which are primed to specifically recognize and target cancer cells expressing the antigen targeted by the CAR. The expanded and activated T-cells are then infused back into the patient’s blood. These engineered T-cells are designed to persist and continue their anti-cancer activity. When the CAR recognizes the specific antigen on the surface of a cancer cell, it triggers the activation of the T-cell. Activated CAR-T-cells release cytokine substances and initiate immune responses, leading to the destruction of cells. Additionally, the targeted and specific nature of CAR-T-cells minimize damage to healthy cells. CAR-T-cells can persist in the patient’s body for an extended period providing ongoing surveillance and memory against cancer cells, thus offering the potential for long term protection against disease recurrence. However, keeping in mind the spectrum of infections encountered in CAR T-cell therapy, including bacterial, viral, and fungal infections, understanding the risk factors, spectrum of infections, and implementing appropriate prophylactic measures are essential to optimize outcomes in patients undergoing CAR T-cell therapy [99].

6. Innovative approaches in immunotherapy

In recent years, immunotherapy has witnessed rapid advancements, leading to innovative approaches that are transforming the landscape of cancer treatment. These approaches leverage the body’s immune system to recognize and attack cancer cells, offering new possibilities for improved patient outcomes [100]. Neoantigens are unique proteins present on the surface of cancer cells as a result of mutations. Neoantigens vaccines are personalized vaccines designed to stimulate the immune system specifically against these individualized cancer markers [101]. This approach holds promise for enhancing the precision and effectiveness of immunotherapy. Presently, neoantigen-based tumor vaccines primarily consist of peptides, DNA, RNA, and dendritic cells, tailored to the unique profiles of individual patients. The notable immunogenicity of neoantigens enables these vaccines to stimulate and proliferate antigen-specific CD4+ and CD8+ T-cells, thereby enhancing the immune response against tumors [102]. Beyond neoantigen vaccines, there is ongoing research into developing broader cancer vaccines that target shared tumor-associated antigens [103]. These vaccines aim to train the immune system to recognize and attack common features present in various cancer types, providing a more off-the-shelf solution. Oncolytic viruses are engineered or naturally occurring viruses that selectively infect and destroy cancer cells. These viruses not only cause direct lysis of cancer cells but also stimulate the immune system by releasing tumor antigens. Talimogene laherparepvec (T-VEC) is an example of an oncolytic virus used in the treatment of advanced melanoma [104]. Administered through direct intratumoral injection, T-VEC initiates both local and systemic immunologic responses. This process aims to induce tumor cell lysis, resulting in the release of tumor-derived antigens and the subsequent activation of tumor-specific effector T-cells. Currently, T-VEC is under evaluation in combination with other immune checkpoint inhibitors like ipilimumab and pembrolizumab, and there is intriguing confirmation of activity, even at the systemic level [105].

In addition to CAR-T-cell therapy, which involves genetically modifying T-cells with chimeric antigen receptors, other adoptive cell therapies are emerging. This includes T-cell receptor (TCR-T) therapy, where T-cells are engineered to express specific TCRs for cancer antigens [106]. As research in this domain advances, insights
into discovering and cloning personalized TCRs specific to tumor antigens are emerging, employing cutting-edge techniques [107]. Despite progress, enhancing the anti-tumor effectiveness of TCR-T immunotherapy faces challenges. These include safely elevating therapeutic TCR avidity, identifying shared tumor-specific antigens and TCRs in patient populations, applying personalized TCRs in cancer patients, and understanding the interactions or signals that regulate TCR expression and function optimally [108]. There is increasing recognition of the role of the gut microbiome in influencing responses to immunotherapy [109, 110]. Modulating the microbiome through prebiotics, probiotics, or faecal microbiota transplantation is being explored as a strategy to enhance the efficacy of immunotherapies [111, 112].

Artificial intelligence and machine learning are being employed to analyse vast amounts of patient data, predict responses to immunotherapy, and identify potential biomarkers. Interestingly, integrating artificial intelligence (AI) and machine learning algorithms (MLA) to analyse complex datasets, including genetic and imaging data, also holds promise for identifying novel predictive factors and optimizing treatments strategies for checkpoint inhibitors [113, 114]. Currently, many predictive models based on AI and MLA algorithms have emerged due to the development and popularization of digital images worldwide and each model or algorithm has its strength and weakness [114, 115]. Attempts are being made in researches for predicting mutations via such approaches to advance precision oncology [116]. These technologies contribute to the development of more personalized and effective treatment strategies. Moreover, researchers are exploring the power of combining different immunotherapies or combining immunotherapy with other treatment modalities such as chemotherapy or radiation therapy. Combinatorial approaches aim to address the complexity of the tumor microenvironment and overcome resistance mechanisms.

7. Resistance mechanism and overcoming challenges

Resistance mechanisms pose significant challenges in cancer treatment, particularly in the context of targeted therapies and immunotherapies [117, 118]. As cancer cells evolve and adapt, they can develop mechanisms to evade the effects of treatments, leading to reduced efficacy over time. In the case of targeted therapy resistance, cancer cells may develop genomic alterations and acquire mutations that alter the target of the therapy, rendering it ineffective. Other than this, cells can also activate alternative signalling pathways to bypass the targeted pathway. In immunotherapy resistance, tumor cells may downregulate or lose expression of the targeted antigens, evading recognition by the immune system. Immunosuppressive cells and molecules in the tumor microenvironment hinder the activity of immune cells. Resistance developed during chemotherapy is another nuisance to drug efflux and DNA repair mechanisms [119]. Cancer cells may develop pumps that actively remove chemotherapy drugs from the cell [120]. Further, enhanced DNA repair capabilities in cancer cells can counteract the damage caused by chemotherapy [121]. Heterogeneity is another form of resistance mechanism of cancer cells [122, 123]. Over time, selective pressure can lead to the dominance of resistant clones within the tumor [124].

Overcoming these challenges requires a comprehensive understanding of the underlying resistance mechanisms and the development of strategies to counteract them. For instance, using drug combinations that target multiple pathways can reduce the likelihood of resistance emerging. Studies have shown that combining different immunotherapies with other modalities can enhance the overall anti-cancer response [125]. Adaptive treatment strategies can also be employed in which treatment schedule adjustment, such as intermittent dosing, may help prevent or delay the onset of resistance [126, 127]. Recently drug cycling has gained recognition. It involves rotating between drugs which can limit the adaptation of cancer cells to a specific treatment [128]. Using personalized medicines is gaining popularity over resistance challenges. Identifying predictive biomarkers helps tailor treatments to the individual patient, increasing the likelihood of treatment success. Moreover, circulating tumor DNA can be monitored through liquid biopsies enabling real time assessment of tumor evolution and the emergence of resistance [129]. Overcoming immunotherapy resistance is a major challenge. Researchers have tried combining checkpoint inhibitors to target different pathways with the aim of enhancing T-cell activation. Strategies to alter the immune-suppressive microenvironment, such as depleting regulatory T-cells, are under investigation. In addition to these strategies, developing new drugs that target resistance mutations or alternative pathways can overcome acquired resistance. The therapeutic effect can be further enhanced by engineering antibodies to simultaneously target multiple antigens or cells.

8. Conclusion and future prospective

In the realm of cancer treatment, the challenges posed by resistance mechanisms underscore the complexity of the disease and the need for innovative therapeutic strategies. Targeted therapies, immunotherapies, and traditional treatments face the hurdle of cancer cells evolving and adapting to survive. While advancements have been made in understanding resistance mechanisms, successfully overcoming these challenges requires a multifaceted and personalized approach. Combination therapies that target multiple pathways simultaneously have emerged as a promising strategy to mitigate resistance. The integration of immunotherapies, such as checkpoint inhibitors and CAR-T-cell therapies, has ushered in a new era of cancer treatment, demonstrating unprecedented successes, especially in haematological malignancies. Personalized medicine, guided by predictive biomarkers and liquid biopsies, enables tailored interventions that consider the unique genetic and molecular profiles of individual patients. The future of cancer treatment lies in continued research and development, focusing on novel agents that can address emerging resistance mechanisms. Advancements in technologies like artificial intelligence and machine learning hold the potential to unravel complex biological interactions, identify new therapeutic targets, and predict treatment responses with greater accuracy.

Ongoing research holds promising prospects in cancer treatment through immunotherapy. Refining the implementation of precision medicine through the identification of additional biomarkers and the integration of omics data can enable more precise and effective targeting of cancer cells. Further optimizing immunotherapies, including the development of new CAR-T-cell constructs, exploring ad-
ditional immune checkpoints, and enhancing strategies to modulate the tumor microenvironment can contribute to improved outcomes. Further, the microbiome’s impact on treatment response needs to be understood and harnessed for enhancing therapeutic efficacy and overcoming resistance. The development of next-generation targeted therapies that address resistance mutations, exploit synthetic lethal interactions, and target alternative pathways can expand the therapeutic options for patients. Patients-centric approaches need more focused research. It involves considering individual patient characteristics, preferences and quality of life in treatment decisions, ensuring a holistic and personalized cancer care experience. Ongoing innovation in clinical trial design can expedite the translation of scientific discoveries into clinically meaningful advancements.

In conclusion, the future of cancer treatment holds great promise, driven by a commitment to unraveling the intricacies of resistance, harnessing the power of the immune system, and advancing personalized therapeutic strategies. Through continuous research, collaboration, and the integration of cutting-edge technologies, immunotherapy aims to redefine the paradigm of cancer care, offering hope for improved outcomes and a brighter future for patients facing this challenging disease.

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