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REVIEW

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Cancer immunotherapeutics: Transforming T-cells to superior cancer killers

Swati Mishra

Department of Zoology, College of Basic Sciences and Humanities, Orissa University of Agriculture and Technology, Bhubaneswar, India

ABSTRACT

The evolution of cancer treatment has marked a significant shift from traditional therapies such as surgery, chemotherapy, and radiation to more targeted T-cell-based therapies. The emergence of immune checkpoint inhibitors (ICIs) and gene-editing techniques like CRISPR/Cas9 has revolutionized cancer immunotherapy. Currently, adoptive cell transfer (ACT) therapies, such as tumor-infiltrating lymphocyte (TIL) therapy and chimeric antigen receptor (CAR) T-cell therapy, are giving promising results in melanoma and leukemia, respectively. Challenges occur to infiltrating solid tumors due to their dense stromal network, and abnormal vasculature has become a barrier. Hence, focusing on these strategies to modify cancer vasculature, immune suppression, and chemokines are major goals of current ACTs. The present review provides insight into the emerging cancer immune therapeutics, their advantages, and limitations. Emphasis is given to the recently discovered "superior" T-cells. These cells exhibit a unique ability to recognize multiple cancer-associated proteins effectively, making TIL therapy the future of cancer management.

KEYWORDS

Adoptive cell transfer therapy, Cancer, Immunotherapeutics, Tumor-infiltrating lymphocyte therapy, Superior T-cells

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Introduction

T-cells play a significant role in one's immune system against infections, foreign pathogens, pollutants, and diseases, including cancer [1]. They are highly specialized to target various cells with their recognition ability via receptors on the cell surfaces. T-cells are of two types, helper T-cells and cytotoxic T-cells; helper T cells release cytokines based on the immune response to foreign pathogens and activate other immune cells [2]. Cytotoxic T-cells are the main killer cells that destroy invading pathogens or abnormal cells [1,2].

T-cells are critical to immunity in cancer treatments as they also recognize and eliminate abnormal cancer cells [3]. Cancer cells usually avoid being detected by the immune system in various ways, including inhibiting antigen expression to T-cells or evading cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) immune checkpoint pathways [3]. In cancer, treatments are always researched for better outcomes and with increased efficiency [3]. Over the years, traditional cancer therapies have been overtaken by modern cell-specific immunotherapies wherein T-cells have a promising role. They can overcome the challenges of traditional therapies such as radiation or chemotherapy [4]. Searching for an ideal cancer therapy with improved potency, efficiency, and safety simultaneously comes with various challenges. These include circulation, homing in on the cancer metastatic sites, cancer cell recognition, reducing and eliminating malignancies, increasing anti-tumor responses, and follow-up post-treatment [4].

Ongoing chemotherapy, targeted antibody and drug therapies, and immune checkpoint inhibition have shown significant results in metastatic melanoma, renal cell carcinoma, and non-small cell lung cancer (NSCLC) [5]. Yet, all patients may not have similar positive treatment outcomes or show improved results [5]. Hence, next-generation cancer immunotherapeutics, like T-cell-based therapies, are welcoming and effectively recognize cancer cells with enhanced specificity [6]. T-cell-specific therapies include activation and differentiation of the T-cells that play a vital role in their ability to identify and effectively kill cancer cells [7,8]. Developing T-cell-based cancer therapeutics requires understanding how T-cells can overcome challenges posed by the tumor microenvironment (TME) [9]. The major challenges faced in T-cell activation and differentiation are immune suppression, tumor antigen escape, tumor-associated immunosuppressive cells, metabolic constraints, and limited tumor infiltration [9,10]. Conventional therapies often have the disadvantage of surrounding cellular toxicity and normal cell physiology disruption. T-cell-based therapies utilize the body's immune system. Recently, adoptive cell transfer (ACT) therapy has gained momentum by infusing a patient's laboratory-engineered T-cells to target the cancer cells precisely [11,12]. Two ACT therapies are growing popular and are extensively being researched. Early on, tumor-infiltrating lymphocyte (TIL) therapy succeeded in melanoma, which was also FDA-approved. However, it was challenging to invade solid or epithelial tumors' abnormal intricacies [13]. The next technological breakthrough was genetically engineering T-cells with artificial receptors, Chimeric Antigen Receptors (CARs), that can identify specific surface proteins on cancer cells. This therapy showed excellent efficiency in leukemias and lymphomas but posed limitations due to fewer cancer-specific surface proteins [14,15].

Despite its limitations, T-cell therapy is still preferred in cancer therapeutics, as it has a unique memory ability. Applying this sustained potential of memory for anti-tumor responses is relevant to avoid cancer recurrence [16]. With breakthroughs in gene editing, target identification, and novel receptor designs, T-cells can be re-engineered for future treatments. T-cell-based therapeutics have opened new avenues in immunology, molecular biology, bioengineering,

*Correspondence: Swati Mishra, Department of Zoology, College of Basic Sciences and Humanities, Orissa University of Agriculture and Technology, Bhubaneswar-751003, India, e-mail: swati200693@gmail.com

and clinical areas. Understanding the interaction between T-cells and cancer is vital for therapy development [17]. A fundamental challenge in ACT is the precise recognition of cancer cells. T-cell receptors (TCRs) can target mutational neoantigens, which hold potential. TCRs can identify single-nucleotide mutations that alter a single amino acid within nine of the cancer cell's Human Leukocyte Antigen (HLA). CD8+ T-cells with these TCRs can target these neoantigens, giving cancer cell specificity [18]. Research is also done to infuse isolated T-cells with these TCRs, giving responses that the bulk T-cells could not. Hence, by developing such TCRs, personalized ACT TCR transgenic T-cell therapies can be given to patients with unique mutational cancers [19].

The present review gives insight into how a conventional T-cell of an immune system is transformed slowly over the decade to become the powerhouse of cancer therapeutics. A transition from traditional to more targeted therapies in cancer is focused specifically on cancer immune therapeutics. Also, advances in the two most important ACTs, TIL and CAR T-cell therapies, are discussed. Focus on the recent discovery of "superior" T-cells in groundbreaking research is emphasized where two patients had remission from solid tumors.

Methodology

An extensive narrative review was conducted to collect information on the use of cancer immunotherapies, adoptive cell transfer therapies, tumor-infiltrating lymphocytes (TILs), and chimeric antigen receptor (CAR) T-cell therapy. Google Scholar was the primary source of articles retrieved for the search. Keywords such as cancer immunotherapies, adoptive cell transfer therapies, tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor (CAR) T-cell therapy, and superior T-cells in different combinations were used to perform database searches.

Inclusion criteria

Articles related to T-cell-based cancer therapies, their development, mechanisms, challenges, and prospects published in English between January 2015 to July 2023 were selected.

Exclusion criteria

Articles published in languages other than English, not related to cancer immunotherapy, non-peer-reviewed sources, or articles published before January 2015 were excluded.

Cancer Immunotherapeutics: A Brief History

Cancer immune therapeutics date to the late 19th century when an American-born surgeon and cancer researcher, William Coley, discovered by chance the same. He observed cancer remissions in patients who had bacterial infections. This was a crude form of immunotherapy observed. The 20th century marked the bone marrow transplantation in the 1950s and the interferon therapy in the 1980s [20]. However, modern therapies came in the 2010s with the most significant achievement of introducing T-cell targeted immunomodulators, CTLA-4, and PD/PDL1 inhibitors (ICIs). Before 2010, solid tumors were treated with immune cytokine-based therapies such as interleukin-2 (IL-2) and alpha-interferon (IFN-α), which had poor efficacy and were highly toxic [20, 21].

In 2011, ipilimumab was the first ICI targeting CTLA-4 introduced, while further monoclonal antibodies (mAbs), such as pembrolizumab and nivolumab, targeting PD-1 and atezolizumab and durvalumab targeting PDL-1 where developed [22,23]. Over a decade now, the success of immunotherapy has risen to prominence. For groundbreaking contributions, the 2018 Nobel Prize in Medicine was awarded to James Allison and Tasuku Honjo for their origin of the concept of ICI-based immunotherapy [24].

Apart from the ICIs, adoptive cell transfer therapy (ACT) was another novel strategy. ICI therapy was usually hindered due to pre-existing tumor-reactive T cells [25]. Melanoma and tobacco-associated non-small cell lung cancer (NSCLC) had the disadvantage of endogenous tumor-reactive T cells due to the UV radiation or inhaled carcinogens that caused them. Limited responses to ICI were also observed in pancreatic and colorectal cancer, marking the requirement of tumor-reactive T-cells through ACT for different cancer treatments [26].

From Traditional (T) Therapies to T-Cell Based Therapies: Transition in Cancer Treatment

Recent years have seen cancer treatment evolve from traditional therapies such as surgery, radiotherapy, and chemotherapy to more targeted T-cell therapies. Traditional therapies have remained a constant treatment plan for cancer patients but with broad mechanisms of action; the targeted T-cell therapies are well-known for their critical role in cancer management due to their efficiency and precise targets of treatments [27]. Traditional therapies can be categorized as surgery, chemotherapy, and radiation therapy.

Surgery

Removing large masses of tumors before starting any drug treatments is done for advanced malignancies. Although it may recur, it still reduces the time of drug treatments to be provided along with radiation [27,28].

Radiation therapy

Using high-energy beams to shrink tumors that have metastasized and spread to other areas is helpful. Like chemotherapy, it affects healthy cells, develops skin burns, fatigue, etc [27]. Owing to damage to healthy cells and various side effects of traditional therapies, more targeted therapies based on T-cells emerged by targeting immune checkpoint inhibitors. Molecules of key signaling pathways were also considered, such as BRAF and MEK proteins [29]. BRAF protein is targeted by inhibitors such as vemurafenib and dabrafenib in melanoma patients with BRAF V600E mutation (valine gets replaced by glutamic acid at 600th amino acid position. It has demonstrated rapid regression and increased response. Likewise, MEK inhibitors such as trametinib have shown efficacy in combination with BRAF inhibitors [30].

Precision therapy for cancer also includes targeting immune checkpoint molecules by their inhibitors (ICI), such as CTLA-4 and PD-1 [31]. By directing inhibitory signals to downregulate T-cell activation, ICIs can engage the immune system to act on cancer cells. CTLA-4 and PD-1 are vital T-cell activation and regulation checkpoints and halt the immune response in immunogenic reactions [32]. These molecules are overridden by tumor cells, leading to immune evasion. Targeted monoclonal antibodies are developed as inhibitors to block these checkpoints and inhibit cancer cells. Phase III

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clinical trials comparing anti-PD-1 and anti-CTLA-4 checkpoint inhibitors found that patients treated with nivolumab had a better response (44%) and survival rate (6.9 months progression-free survival), as compared to those treated with ipilimumab (19% and 2.8 months, respectively) [31,32].

Moreover, integrating gene-editing tools such as CRISPR/Cas enhances T-cell therapies' safety, precision, versatility, and specificity by reducing side effects [33]. Combining targeted and immunotherapies also increases efficiency due to the interconnected signaling pathways of the immune system [31, 32]. With both nivolumab and ipilimumab administered together, response rates were even higher (58%), and survival was longer (11.5 months) [31, 32].

Cancer Immunotherapeutics: Insights on Adoptive T-cell Transfer (ACT) Therapies

Adoptive cell transfer (ACT) therapy

T-cell activation and differentiation are the core of cancer immunotherapy. CD8+ cytotoxic T-cells (CTLs) and CD4+ helper T-cells play a vital role in identifying tumor-specific antigens. Antigen-presenting cells (APCs), like dendritic cells (DCs), process these antigens and present them to major histocompatibility complexes (MHCs) to the T-cells [34]. The major interaction between MHC peptides and T-cell receptors (TCRs) activates the T-cells, ultimately producing some effector molecules such as interferon-γ [35]. In the TME, CTLs become exhausted and dysfunctional due to immune-related tolerance and immunosuppression, favoring adaptive immune resistance [34]. Cancer-associated fibroblasts (CAFs), macrophage type 2 (M2) cells, and regulatory T cells (Tregs) can make immunological barriers to CTL-mediated anti-tumor immunity [34]. Consequently, to make durable and efficient anti-tumor immune responses, CD8 + T cells must be primed and activated toward effector CTLs. Essentially, CD8+ T cell priming corroborates innate immune cell activity, such as DCs and natural killer cells (NKs), with CD4+ T cells [34].

A remarkable success was achieved when T-cell receptor (TCR)-directed T-cell therapy was developed [35]. ACT could reprogram T-cell specificity in the laboratory to selectively act on target tumor antigens. ACT origin is rooted in two pivotal clinical observations [36]. First, the correlation of the extent of T-cell infiltration in tumor masses emphasized the treatment response of T-cells in anti-tumor immunity. Second, the success of allogeneic donor T-cells infused during hematopoietic stem cell (HSC) transplantation emphasized the therapeutic potential of T-cell-mediated immune responses against malignancies [37].

Initially, ACT strategies with autologous T lymphocytes were tested by isolating T cells that had invaded primary melanoma lesions (TILs) and then expanding them in vitro with interleukin-2 (IL-2) [35]. Infusing these cellular products, containing an oligoclonal T cell repertoire that includes CD4+ and CD8+ T cells, mediates potent antitumor responses without toxic side effects. Multiple clinical trials involving patients with metastatic melanoma observed an Objective Response Rate (ORR) of 41% [35]. Following these encouraging results, the approach was expanded and applied to patients with other solid tumors with variable outcomes, promising in some cases (for example, sarcoma, cervical cancer, and ovarian cancer) but modest in others (for example, renal, metastatic renal, and colorectal cancer) [35].

Types of ACT therapy

ACT has rapidly evolved since due to gene engineering techniques. This has led to the development of two most important ACTs: tumor-infiltrating lymphocyte (TIL) therapy and chimeric antigen receptors (CAR) T-cell therapy [36]. TIL therapy gave foundations to the ACT approach that involved isolating tumor-reactive T-cells from the tumor masses, culturing them in vitro, and re-infusing them back into patients. It was effective in melanoma. Another approach was engineering or genetically modifying T-cells to express CARs or TCRs that can identify tumor antigens, hence the name [37]. A third novel type of endogenous T cell (ETC) therapy that focuses on naturally occurring tumor-reactive T-cells in the peripheral blood has also been explored. In vitro stimulation with APCs or artificial APCs produces low-frequency antigen-specific T cells. ETC therapy has clinical benefits, such as broader antigen targeting without abundant TIL samples and the ability to create central memory T cells [38].

CAR T-cell therapy

CAR-T-cell therapy was initiated as a novel concept in the 1980s, but it was practically applied in the 2000s. It involved genetically modifying the T-cells to express chimeric antigen receptors (CARs) on the T-cell surface. CARs are synthetic molecules that combine an extracellular antigen recognition domain with an intracellular signalling domain derived from the TCR complex and co-stimulatory molecules such as CD28, 4–1 BB, or OX40 [39]. Preclinical studies with CARs specific to various tumor-associated antigens (TAAs) have been conducted to evaluate their efficiency [36]. This therapy has gained worldwide attention for showing promising results in acute lymphoblastic leukemia (ALL), chronic lymphocytic leukaemia (CLL), and B-cell lymphoma [39]. The Food and Drug Administration (FDA) approved two CAR-T cell therapeutic drugs in 2018. Kymriah™ (tisagenlecleucel), anti-CD19 CAR-T therapy, was produced by Novartis and approved for treating pediatric and young patients with refractory or relapsed (R/R) B cell precursor acute lymphoblastic leukaemia (ALL) [36]. Yescarta™ (axicabtagene ciloleucel), produced by Kite's company, is another anti-CD19 CAR-T therapy approved for treating adult patients with R/R large B cell lymphoma [36]. The therapy's success drove interest towards applying the therapy in glioblastoma [39]. The recent approval of these treatments has evolved the face of cancer medicine. Advantages of CAR-T-cell therapy include a high affinity for recognition of cancer cells, strong signalling to CD3ζ signalling pathway, not being restricted to MHC, and long-time persistence and memory for years [36]. High response rates and reduced relapses are also important features of this therapy [36].

TIL erapy

TIL therapy was developed in 1982 when the father of ACT, Steven Rosenberg, isolated TILs from tumors of mouse models for the first time. He demonstrated a combined therapy with TILs, cyclophosphamide, and IL-2 that improved colon adenocarcinoma in a mouse with hepatic or pulmonary metastasis [37]. TIL therapy involves harvesting infiltrated lymphocytes from the tumors, culturing them, and passaging them in each generation, in vitro. It is then reinfused into the patients for treatment [38]. TIL therapy has been applied for

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treating melanoma, NSCLC, ovarian cancer, Head and neck squamous cell carcinoma (HNSCC), breast cancer, colorectal cancer, and hepatic carcinoma [37]. Solid tumor treatment by TIL therapy, such as in gastric carcinoma and pancreatic ductal adenocarcinoma (PDAC), has shown potential. CXCR3+ cells are linked to gastric carcinoma-enhanced prognosis [37]. CD8+ T-cells and CD20+ B-cells are correlated with PDAC for progression-free survival [37]. A diverse TCR clonality, superior tumor-homing ability, and low off-target toxicity offer TIL therapy with novel advantages in solid tumors compared to other ACTs [38].

ACT persistence and cancer remission

ACT uses one's T-cells for developing and re-engineering them and then infusing them back to the patients. These T-cells are extensively researched for factors influencing T-cell longevity, prolonged in vivo T-cell population expansion, and enhanced anti-tumor responses. These correlate with improved recurrence-free survival and tumor control. ACT persistence is boosted by optimizing conditions that inhibit host immune cells and favor the accumulation of homeostatic cytokines. Certain markers, such as long telomeres co-expression of CD27 and CD28 on TILs, correlate with clinical response [39]. As with CD4 and CD8 cell infusions, CD8 central memory (TCM) lymphocyte enrichment promotes T cell persistence. A subset of early-differentiated T cells, stem cell memory T-cells (TSCMs) maintain their potency in vivo for decades. In vitro expansion of T cells also influences fitness; IL-21 promotes a TSCM phenotype, while IL-7 and IL-15 expand TSCMs. The intrinsic fitness of T-cells aids them in CAR-T cell therapy for early-memory differentiation, and the lack of exhaustion markers also correlates with the anti-tumor activity [40].

Long-lasting memory and protection of T-cells for prolonged survival in the TME

Ensuring a long-lasting effect of T-cells in the TME requires their prolonged survival and memory to possess enhanced anti-tumor effects [41]. This is done by blocking the interactions between the inhibitory receptors and their ligands [41]. Exploiting T-cell exhaustion where these T-cells gradually lose effector functions and expression of inhibitory receptors such as PD-1, CTLA-4, and LAG-3 [42]. Besides this, immunosuppressive subpopulations or soluble cytokines may also hamper T-cell survival, such as Transforming Growth Factor-beta (TGF-β) contributes to local suppression. CD8+ T-cells can be genetically engineered to resist TGF-β for improved tumor sustenance in TME [42].

Generating long-lasting survival and memory is a crucial portion of developing ACT approaches further to counteract the suppressive TME. It requires extensive research on T-cell dysfunction in the TME and its mechanisms [42].

Challenges of solid-tumors

ACT faces its disadvantages in targeting solid tumors due to their dense stromal architecture, abnormal vasculature, and altered chemokines, which hinder T-cell infiltration. Targeting cancer metabolism and chemokines is extensively studied for ACT infiltration. Reprogramming metabolically may impact the TME and the T-cell function [43]. Targeting reactive nitrogen species (RNS) produced by cancer cells in the TME may block its production by recruiting the T-cells. Fucosylation of T-cell surface glycoproteins also affects the infiltration, which can be improved by ex vivo fucosylation. Tumor progression and immunosuppression are mediated by the CXCL12/CXCR4 axis, activated by neoplastic cells and cancer-associated fibroblasts (CAFs). A decrease in tumor growth can be achieved by inhibiting CXCR4 [44].

The intricacies of immune cells, tumor cells, and cytokines for a tumor immune microenvironment (TIME) that challenges immune responses and enhances tumor development. TIME poses an obstacle to CAR-T-cell efficacy [44]. Targeting immunosuppressive cells, cytokines, chemokines, and immune checkpoints will increase the efficacy of CAR T-cell therapy for solid tumors. For example, TR2.41BB receptor co-expression to target both myeloid-derived suppressor cells (MDSCs) and tumor cells will ensure CAR-T cells increased persistence and proliferation [44]. Another strategy is to target cancer vasculature; tumor neo-angiogenesis leads to leaky vessels that prevent immune cell entry. VEGF inhibitors and vascular-targeting peptides facilitate T-cell homing by inhibiting vessel maturation. Exploring the modifications of chemokine receptor expression is another approach to infiltrate into TME. Chemokines such as CCR2, CX3CR1, and CXCR4 can be modified to improve T-cell migration into the TME [45,46].

Genetically engineered T-resident-memory (TRM) cells are developed that are innovative. TRM cells are permanent tissue-resident T cells that can cause immune reactions; when manipulated or induced, these cells may amplify anti-tumor responses [47]. Anti-cancer vaccines promoting TRM induction show promising results in inhibiting tumor growth and protecting distant sites [47]. Hence, overcoming these barriers is crucial to T-cell homing in solid tumors that will yield efficient results. The discussed approaches may enhance ACT's anti-tumor effects and provide potent therapeutic options in solid tumors.

"Superior" T-cells: a groundbreaking leap in solid tumor treatments

On 24 July 2023, a novel type of killer T-cell was identified in patients who had cleared late-stage solid cancers. This research was published in the Cell Journal. Dominant T-cells were discovered with a unique ability to recognize multiple cancer-associated targets simultaneously. Professor Andy Sewell of Cardiff University's School of Medicine has led the research, and Dr Garry Dolton is one of the lead authors of the published article [48].

The teams found "multipronged" T-cells with superior properties that attack cancer cells using multiple approaches simultaneously. In a clinical trial (phase I/II) with 31 patients that lasted for a decade, TIL therapy was given, and all the TIL cells were T-cells. They analyzed their blood cells, which had successfully cleared end-stage solid cancers. They discovered that these blood cells from cancer survivors showed strong killer T-cell responses to their cancer even after a year they had cleared it. Further, they identified the mechanisms by these cells distinguishing cancer cells from healthy cells [48]. The ability of these T-cells to simultaneously identify multiple cancer-associated proteins revealed that they could respond to many types of cancer at once. These findings may be corroborated with future extensive research to confirm multipronged T-cells association with complete cancer remission. As the research was conducted in a small group of

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cohorts, future explorations require working with a larger population to understand what the anticancer T-cells recognize in patients for full cancer remission [48].

Challenges and Limitations Associated with CAR- T-cell Therapy

Although TCR/CAR-T-cell-specific therapy holds immense potential, limitations are also there. One major limitation is identifying the tumor-specific antigens or biomarkers on the surface of solid tumors that hampers its application to the solid tumor cells. Antigens specific to cancer cells and present on cell surfaces are crucial to enhance the therapy's safety and effects. Second, tumor antigen loss or escape mechanisms pose a risk as the cancer cells may evade T-cell recognition [35]. Adverse effects such as cytokine release syndrome (CRS) and neurotoxicity are also observed. Managing these will ensure patient safety and the feasibility of the therapies [35]. Some other limitations include manufacturing complexity, limited antigen targets, and expensive costs.

Challenges and Limitations Associated with TIL Therapy

While TILs show promising results, their effectiveness varies depending on the type of tumor. In addition, it was difficult to isolate T cells from immune-cold tumors. TILs had low reactivity, especially in tumors with small mutational burdens, and exhibited a low frequency of tumor-specific T cells [35]. The tumor mutational burden of melanoma enriched the pool of tumor-specific T lymphocytes, which contributed to its success with TILs. TILs were stimulated in vitro with immunogenic cancer epitopes from circulating T cells from patients to overcome these limitations [35]. Clinical benefits were observed with selective expansion of tumor-specific T cells. However, TCR affinity and its functionality were unpredictable in these cell populations, which remains a concern [35].

Harvesting and culturing tumor cells for therapy, limited TILs, expensive and specialized infrastructure, prolonged culture time, reduced persistence, and co-stimulation challenges are various limitations of TIL therapy [37]. IL-2-related side effects are also observed, as IL-2 is mostly used to culture and expand TILs. Hence, lower side effects but enhanced efficacy is a challenge [37].

Future Perspectives

ACT therapy is in a new era now with the discovery of "superior" T-cells and shows a promising frontier in cancer immunotherapy. The unique ability to recognize multiple targets by the T-cells, combined with the already known advantages of ACT, provides huge potential in cancer treatments. Further, it may also be tailored to individual patient requirements for personalized therapies [48]. ACTs can be combined with ICIs, modified cytokines, and cancer vaccines to minimize the limitations and expand the efficacy [37]. Multi-omics and sequencing techniques will further standardize a platform to expand these therapies and focus on personalized immunotherapy [37].

Conclusions

The discovery of "multipronged" T-cells that can identify multiple tumor-associated antigens (TAAs) has significantly contributed to cancer therapeutics. These T-cells have superior recognition with their targeting abilities and have become an innovative approach to studying solid tumors extensively. A multi-epitope recognition strategy yields cumulative effects, enhancing cancer cell detection and improving tumor elimination efficiency. This innovative strategy capitalizes on the inherent diversity of TCR interactions with cancer cell-presented peptides and amplifies the prospects of T cell-centric immunotherapies. The previously unknown antigen specificities of successful cancer-specific TCRs used in CAR-T cell and TIL therapies are also explained. The review highlights the importance and advantages of transitioning to T-cell-based therapies focusing on CAR-T-cell and TIL therapies. Although with different challenges and limitations of both therapies, special attention has been given to the recently discovered "superior" T-cells. These superior cells are the new frontiers of treating solid tumors and ensure a progression-free survival that warrants further research.

Disclosure statement

No potential conflict of interest was reported by the author.

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