Cancer Immunology: CAR T-cell Therapy on Renal Cell Carcinoma

Qingyang Huang[1,*] and Song Ying[2,*]
[1]School of Human Nutrition, McGill University, Montreal H9X 3V9, Canada
[2]Department of Health, Kinesiology & Applied Physiology, Concordia University, Montreal H4B 1R6, Canada

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Abstract: Chimeric antigen receptor T (CAR-T) cell therapy is a revolutionary tool for cancer treatment. Studies have shown its potential in treating hematological malignancies. Renal cell carcinoma (RCC) as the most common kidney cancer, would develop malignant tumor in the lining of kidney tubules. It has the highest mortality rate among all genitourinary cancers. The main issue for RCC is its recurrence rate after surgery treatment. As CAR T-cell therapy has shown its benefits in treating the leukemia and lymphomas, its use in RCC is taking in consideration to reduce the chance of recurrence. Currently, there are some clinical trials are ongoing to measure its feasibility. It is also important to pay attention to the CAR T-cell associated toxicities, on-target off-tumor effect and tumor infiltration that would affect CAR T-cell therapy during the clinical trials. This review focused on presenting ongoing clinical trials of CAR T cell on RCC and its limitations. Some future perspectives are introduced to provide goals in later research.

1 INTRODUCTION

Renal cell carcinoma (RCC) is an aggressive kidney disease originates in the lining of tubules. (Motzer, 1996) The ratio for both affected men and women is about 2:1. Other than age and sex, cigarette smoking and obesity are also risking factors. According to studies, for cigarette smokers, the increase in risk for RCC doubles. Obesity in both women and men increases in mortality rate of RCC. (Yu, 1986) Moreover, about 2% of the RCC has hereditary syndrome. (Cohen, 2005) When a first-degree family member has RCC, the risk for the second-degree family member would be fourfold. (Motzer, 1996) Generally, clear cell renal cell carcinoma (ccRCC) is one of the typical RCC which represents around 3/4 of the cases. However, some patients would develop the advanced RCC including locally invasive or metastatic RCC (mRCC) as the cancer cells would spread with a fast speed in the body. (Cohen, 2005)

Normally, surgery resection is the only effective treatment for renal cell carcinoma because of its chemoresistance. The patient would need to remove the cancer cell affected kidney or having a kidney transplant. Partial and radical nephrectomy are used to treat localized RCC. For metastatic RCC, it requires systemic therapies which are associated with high mortality. (Hsieh, 2017) The approval of cytokine-based immunotherapies (IFN-a and IL-2) and tyrosine kinase inhibitors (TKIs) show effect on reducing the mortality of metastatic RCC. (Schepisi, 2020) Other treatment including radiation therapy and arterial embolization as the palliative therapy are for patients who cannot have surgery. Patient's health condition and the stage of RCC are the general factors that affect the chance of recovery and treatment methods. The recurrence rate of renal cell carcinoma after nephrectomy is about 30%. (Chin, 2006)

In recent years, CAR T-cell therapy has become one of the effective cancer treatments. It was originally designed to treat hematologic neoplasms, and have been used to treat solid tumors, including RCC. (Schepisi, 2020) CAR-T cells are T cells that have been genetically modified to create an artificial T cell receptor for use in immunotherapy, which are recombinant cell surface antigen receptors that have changed the specificity and activity of T lymphocytes and other immune cells in the blood. (Curran, 2012) CARs have an extracellular antigen-identifying domain made up of monoclonal antibody fragments that recognize a particular protein on the cell membrane of malignant cells and an intracellular stimulating region that triggers CAR T-cell activation and activity by signaling through the T-cell receptor (TCR). (Minutolo, 2019) T cells must grow before they can be used for CAR transduction and

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amplification. In this process, transduction can take many forms, but in clonal growing and durable T cells. Based on this principle, CAR can target antigens expressed on the cell surface, as well as various T cell subpopulations, T cell progenitors, and other immune cells.

CAR T-cell therapy is also known as a "living drug," since its effects might last for years. Because the cells may live in the body for a long period, they may be able to detect and target cancer cells if and when they reoccur. (Sadelain, 2013) Importantly, CARs with high potential and signaling quality can control T cell proliferation and persistence, as well as the degree of engineered T cell activation in the cancer microenvironment, both of which are traits that have a significant impact on cancer-targeted T cell effectiveness and safety. (Watanabe, 2018) Nowadays, techniques have been implemented to improve cancer treatment for solid tumors, primarily by overcoming challenges posed by T cell features and the tumor environment. Companion diagnostics, such as IHC and CTC detection tests, can be used to improve CAR T-cell therapy of solid tumors. (Ma, 2019)

Therefore, to overcome this hurdle, CAR T-cell treatment show its prospect in treating RCC. This review summarizes the current CAR T-cell treatment clinical trials on renal cell carcinoma and its limitations. Moreover, the future perspectives for the use of CAR T-cell therapy on RCC are explored.

2 CURRENT TRIALS OF CAR T-CELL THERAPY ON RENAL CELL CARCINOMA

For decades, surgery has been the only effective treatment because of its chemoresistance. To overcome this hurdle, CAR T-cell therapy shows its advantages in treating tumors compared to the previous modalities of adoptive cell therapy such as TCR and TIL. Unlike TCR and TIL, CAR T-cell therapy is a non-MHC-restricted approach, therefore it can target the tumor cells without recognition of MHC, as most of cancer cells would trigger the loss of MHC expression to escape the T-cell immune response. (Rohaan, 2018) Currently, FDA has approved CD19 CAR T-cell therapy for Acute Lymphoblastic Leukemia (ALL), Diffused large B-cell lymphoma (DLBCL) and many other NHL. Although there is no CAR-T cell therapy for RCC approved by FDA right now, some clinic trials are still ongoing.

2.1 CAR T-cells CCT 301-38 or CCT 301-59 in Relapsed /Refractory Stage IV RCC

The recent clinical trial evaluates the safety and efficacy of the two autologous CAR T-cell CCT301-38 and CCT301-59 with escalation and expansion on does. CCT301-59 targets the neurotrophic tyrosine kinase, receptor-related 2 (ROR2), as the CCT301-38 directed against *AXL* gene expression. In patients with kidney cancer, *ROR2* expression is associated with genes responsible for mitosis and metastasis. *AXL* gene is involved in cell proliferation, angiogenesis, immunity, stem cell maintenance and other therapeutic processes. A total of 66 patients participated in the clinical trial. Patients who tested positive for *ROR2* were treated with CCT301-59, while patients who tested positive for AXL but negative for *ROR2* were treated with CCT301-38. Peripheral blood mononuclear cells (PBMCs) are needed to produce CCT301-38 and CCT301-59. During the production of CCT201-38 and CCT301-59, the trial requires patients to undergo a conditional chemotherapy of regiment of cyclophosphamide and fludarabine for lymphodepletion. After the injection of CCT301-38 or CCT301-59 to After depleting lymphocytes, patients would intravenously inject one dose of CCT301-38 or CCT301-59. The estimate primary completion date for these phases I and II trials are in June 2022. (ClinicalTrials.gov, 2018)

2.2 CAR T-cell Therapy with PARPi

This research shows the application of CAR T-cell therapy on targeting CD70 is through introducing a single chain antibody against CD70 and generation of CD70 CAR-T cells that have an effective anti-tumor function both in vitro and vivo. (Ji, 2021) Moreover, the PARP inhibitor (PARPis) is used to enhance the effectiveness of this CAR T-cell therapy by increasing the recruitment of CD8+ T cells to the TME in this trial. The second-generation humanized CAR was first used to augment its anti-tumor efficacy. (Pantelidou, 2019) The introduction of PARPi olaparib (OLA) to CD70 CAR T-cell therapy in RCC show its effects on promoting the apoptosis of RCC cells but protecting CAR-T cells from apoptosis. It also shows a more effective repression of RCC cells with a better survival rate. The OLA-mediated CAR T-cell therapy starts with the cGAS/STING signaling pathway, which is a key activator for PARPi treatment to promote infiltration of CD8+ CAR T-cell. It then up-regulates the IFN-B expression and the expression of both CCL5 and

CXCL10. Both would improve the amount of CD8+ CAR T-cells and enhance the tumor lysis due to the secretion of granzyme B. These demonstrated that cGAS-STING pathway determines the Penetration and permanence of OLA-mediated CAR T-cell therapy in TME. This approach shows its potential in treating the solid tumors. (Ji, 2021)

2.3 Metastatic Renal Cell Carcinoma with CAIX CAR-engineered T cells

Metastatic renal cell carcinoma (mRRC) is well known for its treatment-resistance. The patients with mRRC often with poor survival of less than one year after diagnosis. (Gupta, 2008) Therefore, the CAR T-cell therapy is applied to treat mRRC. However, CAR T-cell therapy may develop a toxicity in the body due to its "on-target" effect. Carbonic anhydrase-IX (CAIX) is a transmembrane protein that is over-pressed in RCC. It is generally used as a diagnosis marker or drug target. In the trial, 12 mRCC patients with CAIX-pressing were injected by CAR-T cell that is engineered against CAIX. The patients would pre-treat with a CAIX monoclonal antibody (mAb) G250. The results indicate that there are no toxicities in the liver. Moreover, this trial surprisingly enhances the T-cell persistence in the therapy. Therefore, by pre-treating patients with CAIX mAb, it helps to prevent on-target toxicity from CAR T-cell therapy on RCC and improve the peripheral persistence. This strategy can be applied on the use of CAR T-cell therapy in other cancer. More research is needed. (Lamers, 2013)

3 LIMITATION

CAR-T cells binding to target antigens expressed on the cell surface is independent of MHC receptors. It caused T cell activation and a powerful antitumor response, which is revolutionary for leading a remarkably effective and long-lasting clinical response. When targeting solid tumors, CAR-T cells have shown mild clinical efficacy in malignancies. (Neelapu, 2017) The development of T cell in vitro growth technology and genetic engineering enables the rapid generation of tumor antigen effector cells, which promotes the applicability of cancer immunotherapy. However, the serious toxicity of CAR T-cell therapy, targeting of non-tumor cells, cell metastasis and tumor invasion remain unresolved.

3.1 CAR-T cell-associated Toxicities

CAR-T cells recognize hLA-independent and reduce the risk of cross-reaction by binding to larger epitopes. (Casucci, 2014) Genetic engineering may improve the toxicity characteristics of traditional chemotherapeutic drugs by improving the accuracy of T cell recognition of targets. Nonetheless, cell therapies are unique in that up to 10 years of extraordinary long-term persistence can be achieved using adoptive cellular therapy in human trials. The timeline for this persistence will potential toxicity to extend far beyond traditional small-molecule drugs timeline. (Scholler, 2021) Side effects after CAR T-cell therapy may be rapid, slow, moderate, severe, and even persist throughout the T cell cycle, thus preventing the development of CAR T-cell therapy. Data showed that nearly all patients with acute lymphoblastic leukemia and lymphoma treated with CAR-T cells had at least some mild toxicity, while 23-46% showed production of parapsychological cytokines and severe in vivo T cell proliferation. (Frey, 2016)

Cytokine release syndrome (CRS) is a systemic inflammatory response that leads to immune activation caused by exogenous cytokines produced by CAR-T cells, leading to dysfunction in most organs. (Lee, 2014) Specifically, patients with leukemia (77-93%) and with lymphoma (67-91%) treated with CAR-T cells experienced more CRS of any grade, compared with patients treated with axicabtagene ciloleucel and tisagenlecleucel for relapsed or refractory B-All. (Halford, 2020) CRS-associated cytokines may be produced directly by injected CAR-T cells or macrophages, which may produce cytokines in response to injected CAR-T cells. (Brudno, 2016)[24] And elevated serum levels of several cytokines, including interleukin-2 (IL-2), IL-2, IL-2-receptor -α, IL-8, IL-10, tumor necrosis factor and so on, are associated with fever, tachycardia, hypotension, and other toxicity after CAR-T cell infusion. The severity of CRS and the increase of serum cytokines are associated with the disease burden, and the higher the disease burden, the greater the toxicity. Clinically, the characteristics of CRS ranging from mild to severe include fever, creatine, aversion to eating, rapid heartbeat, decreased blood pressure, increased capillary osmotic pressure, loss of cardiac function, abnormal renal function, weakened liver function, and disseminated coagulation in the blood vessels. (Bonifant, 2016) Patients in clinical trials of CAR-T cells often develop neutropenia and lymphocytopenia after chemotherapy and CAR-T cells. After CAR-T cell

infusion, bacteremia, salmonella, urinary tract infections, and viral infections such as influenza, respiratory syncytial virus, and shingles virus have been observed. (Brentjens, 2010) Besides, elevated cerebrospinal fluid cytokine levels can induce ICANS presenting with delirium, encephalopathy, aphasia, drowsiness, inattention, agitation, tremors, seizures, and rare cerebral edema.

3.2 On-Target off-Tumor Effects

Solid tumor antigens are usually expressed at different levels in normal tissues, so antigen selection is critical for CART engineering, not only to protect the therapeutic effect, but also to inhibit the extratomatous cross-reaction of overactive toxic engineered T cells. Exposure of high doses of CAR-T cells to heart, lung, or liver tissue at the time of initial cell injection leads to rapid death. Even if the tumor is successfully targeted, a rapid increase in overall T-cell activity driven by CAR signals during treatment may result in tumor-lysis syndrome, which rapidly removes large numbers of tumor cells in a short period of time, endangering cell life. The differences between patients in T cell response and risk of toxicity make it challenging to predict the optimal number of T cells to be transfused. (Morgan, 2010) Therefore, allowed to control the regulation of the dose and time T cell function of system engineering is an important priority. (Sadelain, 2013)

3.3 CAR-T cell Trafficking and Tumor Infiltration

Compared with hematological malignancies, CAR T-cell therapy in solid tumors is limited by the ability of CAR T cells to transport and infiltrate solid tumors because of physical tumor barriers such as immunosuppressive tumor microenvironment and tumor stroma that limit CAR T-cell penetration and mobility in Figure 1. (Murad, 2018) After infusion, CAR-T cells need to enter the malignant site, navigate the complex tumor environment, form effective interactions with cancer cells, exert their cytotoxic activity, and ultimately persist. Many immunosuppressive cells can infiltrate solid tumors in the tumor microenvironment, including medullary suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs), which promote the production of cytokines, chemokines, and growth factors. In addition, immune checkpoint pathways such as PD-1 or CTLA-4 can be used to modulate antitumor immunity, causing T cell dilation and short-term T cell persistence, resulting in less effective CAR T-cell therapy. (Quail, 2013) Furthermore, increased tumor hardness, an increased deposition of tumor ECM proteins and the significant presence of cancer-associated fibroblasts have been shown to promote immunosuppression through various mechanisms. More simply, the thick network of collagenous fibers surrounding some tumor islets may constitute a physical barrier to t-cell lymphocyte invasion of tumor cell regions. (Yamauchi, 2018)

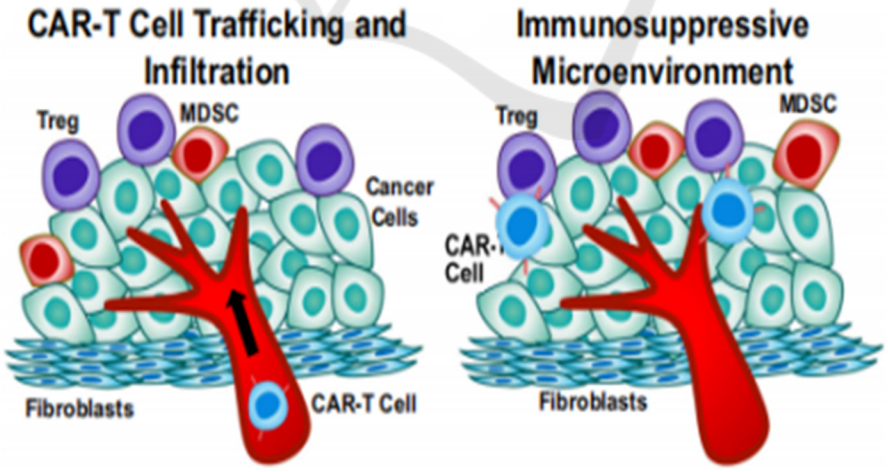

Figure 1: Tumor metastasis and invasion and immunosuppressive tumor microenvironment. (Sterner, 2021) CAR-T cell trafficking to tumors may be hampered by aberrant tumor blood vasculature with pericyte detachment, deregulation of chemokine-chemokine receptor interaction, extracellular matrix (ECM) protein deposition by cancer-associated fibroblasts (CAF), MDSCs, Tregs, and encounters with TAMs.

4 FUTURE DEVELOPMENT

4.1 Reduction of CAR-T cell-associated Toxicities

Cytotoxicity can be reduced by altering the affinity of CAR-T cell antigen binding domains. In this way, tumor cells can increase their response to higher concentrations of antigen and achieve higher levels of activation. (Sterner, 2021) As a result, decreased antigen affinity is predicted to avoid targeting healthy tissues with low levels of antigen. Compared with antigen binding regions with low affinity, antigen binding regions with micromolar affinity were more selective for tumors with higher antigen expression levels. (Liu, 2015) The 4-1BB domain receptor was associated with reduced toxicity and increased T cell tolerance, while the CD28 costimulatory domain was associated with CAR-T cell activity. The 4-1BB costimulation domain can be specifically targeted at tumors with high burden and antigen density. In contrast, in the low affinity antigen binding domain CAR, the CD28 costimulatory domain may be required to reach the desired T cell activation threshold. (Salter, 2018)

Changes in hinge and transmembrane regions that activate CAR-T cells can also affect cytokine production. For example, CD8-derived hinge and transmembrane amino acid sequence changes can reduce cytokine levels and reduce THE proliferation of CAR-T cells targeting CD19 CAR93.These improved hinged and transmembrane region CARs resulted in complete remission in 50% of B-cell lymphoma patients in a Phase 1 clinical study, so optimizing these domains may be an effective way to reduce toxicity. (Ying, 2019)

4.2 ON-Switch Control Mechanisms

Adoptive transfer of T-cells expressing the CAR has yielded extraordinary in the treatment of B-cell malignancies. Other cancers are less responsive to this technique. In the case of solid tumors, CAR T-cell metabolic fitness must be ideal in order for them to reach the tumor and carry out their cytolytic activity in an often-hostile environment. (Pellegrino, 2020)

However, there is a risk that shutting off all CAR-T cells in a patient may allow residual tumor cells to proliferate unregulated and fast. A mechanism was discovered to switch off CAR-T cells selectively, using a small molecule-controlled caspase that promotes T cell death. (Ciceri, 2009) Another way to supplement is to keep the cells dormant until the small molecule drug signalling is introduced (Fig. 2). This ON switch provides for titratable T cell activity regulation (dial-up or down). When certain "no-kill" ligands are found, another strategy is to develop negatively regulated co-receptors that can overcome the death response. (Fedorov, 2013)

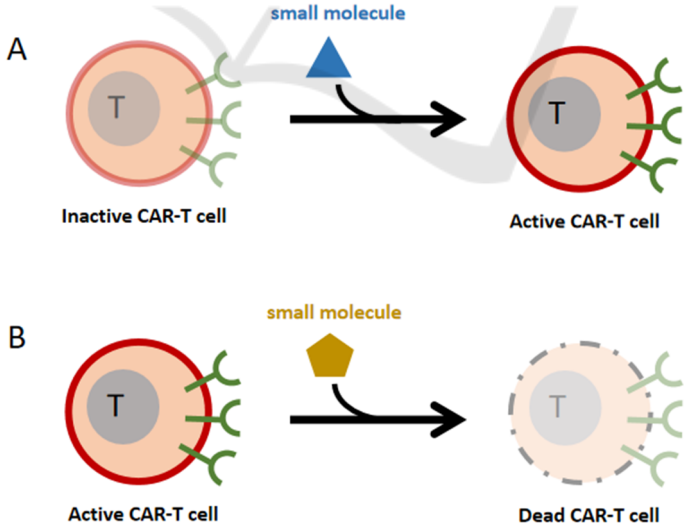

Figure 2: ON-switch control mechanisms. (Wu, 2015) (A). The small molecule medication signal is used to trigger CAR-T cell active. (B). CAR-T cells are switched off selectively using a tiny chemical that causes T cell death.

4.3 Improvement of CAR-T cells Trafficking

Tumor and T cell metabolism, via modulating tumor microenvironment and T cell destiny and activity, have now been discovered to function in determining immune response. CAR-T cell treatment can be enhanced by focusing on this element. The expression of chemokine receptors on CAR-T cells is a recently established technique that looks to dramatically increase CAR-T cell trafficking. (Whilding, 2019) In animal models, CAR-T cells targeting the fibroblast activating protein (FAP) exhibited improved cytotoxic efficacy by decreasing tumor fibroblasts. (Wang, 2013)

5 CONCLUSION

CAR T-cell therapy on RCC has showed its effect in treating the solid tumor or reducing the "on-target" effect. However, its limitation still needs sustainable investigation to improve the efficacy. Currently, some studies have given ideas to reduce its toxicity and improvement of trafficking. Therefore, these methods may take in consideration for their application on CAR T-cell therapy on RCC. The approval of designated CAR T-cell therapy for specific cancer has confirmed its importance in certain tumors as the first-line treatment. It is encouraging to have more CAR T-cell therapy related to cancer treatment to broaden the horizons.

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