Current and Future Perspectives of CAR T-Cell Therapy in Pancreatic Cancer

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Abstract. One of the deadliest cancers in the world is pancreatic cancer with contributing factors resulting from late diagnosis, rapid disease progression, and limited effective therapies. Fortunately, in recent years, immunotherapies like chimeric antigen receptors (CAR T-cells) have become very effective and successful in the treatment of hematologic cancers. With these favorable results, researchers are focusing on using CAR T-cells for solid cancers. This review examines some of the recent pre-clinical and clinical studies conducted over the past few years on promising targeted antigens for CAR T-Cells in pancreatic cancer, including but not limited to mesothelin, Claudin18.2, CD318, and PSCA. While these antigen CAR T-Cells showed positive results, multiple limitations reduce the effectiveness of the treatment. These major barriers include suppressive tumor microenvironment (TME), antigen loss and heterogeneity, or toxicity. Nonetheless, researchers continue to investigate new target antigens and strategies that could overcome these barriers and enhance the therapy's safety and outcome like novel CAR designs.

Keywords: CAR T-Cells; Pancreatic Cancer; TME.

1. Introduction

As of 2025, pancreatic cancer is ranked the sixth most common cancer-related death, with around 500,000 deaths per year. Every year, pancreatic cancer cases continue to increase rapidly, with a relatively low survival rate and high recurrence rate. Of those diagnosed with pancreatic cancer, the five-year survival rate is around 10% globally [1]. There are multiple risk factors, including smoking, family history, genetic predisposition, obesity, and other factors which can contribute to the accumulation of genetic mutations and eventually cause uncontrolled proliferation of abnormal cells. While it is treatable in its early stages, it often poses challenges of detecting it in its early stages with early symptoms similar to those of other illnesses [2]. According to the National Library of Medicine, over 80% of pancreatic cancer patients are at the regional or distant stage when diagnosed, associated with stage 3 or 4 pancreatic cancer [3]. Furthermore, there is a lack of treatment that could effectively fight against metastasized pancreatic cancer, with the main options being chemotherapy, surgery, or radiation [2]. These reasons contribute to the unfavorable outcome of pancreatic cancer.

However, in recent years, immunotherapies have shown a promising future of becoming a novel treatment option that could help enhance our body's immune system to fight pancreatic cancer [4]. Specifically, CAR T-cells have made significant advancements in hematologic cancers – malignancies that begin in the blood or bone marrow, including leukemia, lymphoma, and multiple myeloma. Researchers are looking into CAR T-cells in hopes that could be used to increase the survival rate of solid cancers [5]. This paper reviews the possible treatment of pancreatic cancers, especially CAR T-Cells: discussing the outcomes of recent pre-clinical and clinical trials, their challenges and limitations, and exploring future expectations.

2. CAR T-Cells

CAR T-cells or chimeric antigen receptors are T lymphocytes that are extracted from patients and are genetically modified to express CAR receptors. Essentially, their intended purpose is to identify and attach to tumor-associated antigens (TAAs) expressed on the surface of cancerous cells and directly kill them by releasing cytotoxic chemicals and cytokines. The CAR receptors are composed

of three main components: the extracellular domain (also known as ectodomain), a transmembrane domain, and an intracellular domain (also known as endodomains). The extracellular domains are made up of a single-chain Fragment variant (scFv) that binds to TAAs and helps recognize the tumor cells. The transmembrane domain lies in the membrane, and it brings stability to the receptor. Lastly, the intracellular domains send signals to activate the T-cells upon cancer cell antigen recognition [6].

There are currently six CAR T-cells approved by the US Food and Drug Administration (FDA) that treat hematologic cancers. Reports from clinical trials have confirmed the efficacy of the CAR T-cell treatment, with a significant increase in patient survival. For example, the 4-year survival rate of large B-cell lymphoma increased from 54.6% to 46.0%. This advancement has prompted researchers to continue investigating the possibility of using CAR T-cell therapy in solid tumors, including pancreatic cancer [7].

3. Pre-Clinical and Clinical Trials

Researchers have identified multiple possible antigens in pancreatic cancers that could be targeted by CAR T-cells, including mesothelin, Claudin18.2, CD318, and prostate stem cell antigen. All are shown to be promising as these targeted antigens are often overexpressed on the PDAC tissues but minimally expressed in healthy tissues.

3.1. Mesothelin (MSLN)

MSLN is a TAA that is overexpressed in many different cancers. Particularly, this was one of the first antigens identified and tested in pre-clinical trials for CAR T-cells in advanced pancreatic ductal adenocarcinoma (PDAC). In one of the clinically successful trials, MSLN CAR T cells were injected into a group of mice bearing pancreatic cancer cells. In their findings, a significant number of mice showed complete remission [8].

However, toxicity and immunosuppressive (TME) remain a concerning challenge [9]. Researchers have tried different methods to enhance the MSLN CAR T-Cell. One of the methods can be seen in a clinical trial published by the National Library of Medicine in May of 2024. During this trial, the researchers engineered an anti-mesothelin CAR T-Cell that also secretes a T-Cell engaging antibody molecule (TEAM). This molecule targets the CAFs in the TME by binding to the fibroblast activation protein (FAP) present on their surface. The results demonstrated a positive outcome with an increased reduction of PDAC [10].

3.2. Claudin18.2

Another promising targeted antigen is Claudin18.2. During one of the successful clinical trials, a 72-year-old man with metastasized PDAC received Claudin18.2 CAR T-Cells after chemotherapy and pancreaticoduodenectomy treatment was ineffective. In this trial, the patient experienced a complete response 1 month after treatment and stayed in remission for about 8 months. However, the patient also developed a grade 2 cytokine release syndrome (CRS) and gastric mucosa injury [11]. Considering this, necessary changes are still needed to address the toxicity and the eventual relapse of PDAC. The efficacy of Claudin18.2 is still being tested in preliminary stages, and larger clinical trials are required to verify its effectiveness. Nonetheless, the trial's positive results still showed how Claudin18.2 CAR T-Cells may be an effective method to treat advanced PDAC.

3.3. CD318

Similarly, CD318 (also known as CDCP1) has been shown to be another possible targeted antigen found in PDAC. Pre-clinical studies done in vitro and in mouse xenograft models have demonstrated its effectiveness with increased immune cells within the TME and efficient target cell killing. Furthermore, there were minimal on-target, off-target toxicity signals found [12]. Researchers are anticipating CD318 to be a reliable target for the use of CAR T-Cells in PDAC. However, most of these findings are only supported by pre-clinical trials, and many of the clinical trials are still in testing.

For example, there is a clinical trial of CD318 CAR T-Cell at the University Hospital Tuebingen, and the study is estimated to be completed in 2028 [13]. Additional research is necessary to confirm the efficacy of this therapy.

3.4. PSCA

PSCA is a glycoprotein often overexpressed in pancreatic cancer. In a pre-clinical study done on mouse xenograft models, the second generation of anti-PSCA CAR T-Cells showed a strong anti-tumor response to PDAC when it was administered along with IL-2. There was a significant reduction in the tumor, and two of the five mice in the study showed complete tumor eradication. Additionally, it has also been observed that the difference between the PSCA expressed on normal pancreatic tissues and PDAC is 1000-fold. The low expression PSCA on the healthy tissues suggests that it may have a lower risk of on-target, off-target toxicity compared to the other antigens [14]. Still, these results may be reflected differently when tested on humans. Similarly to the other antigens discussed, there are limited clinical trial outcomes or data that reflect upon efficacy. Therefore, further testing and studies are needed for PSCA CAR T-cells to become a possible treatment method.

4. Barriers to Effective CAR T-Cell Therapy in Pancreatic Cancer

4.1. TME

TME is a complex environment surrounding the tumor and is often characterized by the lack of nutrients, acidity, and hypoxia, which create an immunosuppressive environment for the immune cells. Furthermore, its surroundings consist of stroma components: blood vessels, extracellular matrix (ECM), fibroblasts, endothelial cells, etc. All these components come together and help the tumor grow, metastasize, and survive under our constant immune surveillance.

The ECM is an extracellular component that is found within other organs and tissues, and it has multiple essential functions, including providing structural support and mediating communication between cells through biochemical and biomechanical signals [15]. Conversely, it contributes significantly to the resistance of CAR T-cell therapy in solid tumors [16]. In the TME, the ECM protects the tumor and helps it progress. The cancer cells and cancer-associated fibroblasts (CAFs) produce and alter the ECM composition through a process called fibrosis. The fibrotic ECM is made up of excessive accumulation of proteins such as collagen I, elastin and fibronectin, and laminin. The high concentration of these components provides a dense and stiff structure around the tumor, creating a physical barrier for T-cells or other therapeutic drugs [17]. As a result, if the patient were to be infused with a large number of CAR T-cells, only a small number would be able to infiltrate the ECM. This makes it difficult for the CAR T-Cells to come into contact and directly destroy the malignant cells.

In addition to the ECM, there are also immunosuppressive cells in the TME that challenge the CAR T-Cells by creating a hostile environment. They prevent T-cells from becoming activated by releasing inhibitory cytokines and disrupting signaling pathways. For example, regulatory T-cells (Tregs) suppress the immune cells to ensure that other healthy cells are not attacked [18]. However, studies have shown that Tregs in the TME are often correlated with poor outcomes of CAR T-cell treatment in solid tumors. Tregs compete with the CAR T-cells for IL-2, a cytokine that is crucial for the proliferation of T-cells. Additionally, these regulatory T-cells secrete immunosuppressive IL-10 or TGF-β, which inhibits CAR T-Cells from attacking the malignant cell [19]. Over time, this contributes to T-cell exhaustion or the T-cell's inability to respond and eliminate cancerous cells [18].

Overall, the components of the TME create a suppressive environment that prevents the CAR T-cell from carrying out its effector functions, resulting in poor efficacy of the CAR T-Cell therapy.

4.2. Evading Immune Cells

CAR T-cells enable our adaptive immune system to recognize TAAs expressed on the surface of cancer cells. Yet, several significant challenges emerge, such as antigen escape or antigen

heterogeneity. Particularly in solid tumors, antigens may be inconsistently expressed across the malignant cells. This makes it difficult for the T-cells to target and destroy all the tumor cells. Furthermore, following the pressure induced by the therapies, the phenomenon of antigen escape occurs when the malignant cells mutate or lose their antigens. Both present barriers lead to relapses or poor response to the therapeutic treatment of pancreatic cancer [20].

4.3. On-target, Off-target Toxicity

Another one of the major challenges of using CAR T-Cell therapy for solid tumors is the potential side effect of on-target, off-target toxicity (OTOT). It is where the CAR T-cells attack non-malignant cells that express the same target antigen. In terms of solid tumors, many often express the same antigens that are also co-expressed on non-malignant cells. For example, HER2 is often overexpressed on several cancer cells including pancreas, breast, ovarian, etc. However, it can also be found in heart muscle tissue, urinary bladder tissue, breast tissue, etc [21]. This side effect has been observed in several clinical and pre-clinical, while the severity depends on each patient. Referring back to HER2, there was one case in one of the phase 1 studies in which the patient experienced severe gastrointestinal haemorrhage [22].

5. Conclusion

Immunotherapies, including CAR T-cells, have shifted the perspectives of the treatment in pancreatic cancer. Its success in hematologic cancers gave researchers hope in using it for solid tumors. Currently, multiple targeted antigens have shown promising results, such as but not limited to mesothelin, CD318, Claudin18.2, and PSCA. The positive therapeutic response of these antigen-specific CAR T-Cells consists of a reduction or complete eradication of the tumor in mouse xenograft models or the patient experiencing complete remission for a while after receiving treatment.

Yet, many are still under clinical trials, and further studies are needed to ensure their effectiveness. In addition, researchers are still trying to find solutions to the significant barriers that limit the therapy's success. These include the TME, the escaping mechanisms of the tumor, and the possible serious side effects that may come from on-target, off-target toxicity.

One of the new novel innovations the researchers are looking into to combat these barriers is the armored CAR T-cells. Unlike traditional CAR T-cells, armored CAR T-cells express proteins such as cytokines or antibodies alongside the CAR, reducing immunosuppression and enhancing the function of T-cells. An example is the MSLN CAR-TEAM T-Cell as discussed earlier. Some other methods also include the dual targeting t-cells that target two antigens on the malignant cells simultaneously, or CRISPR-engineered CAR T-cells that use CRISPR-Cas9 to edit the DNA inside T-cells. It prevents T-cell exhaustion, reduces the risk of toxicity or other side effects, etc.

Looking ahead, the novel targeted antigens and emerging innovations could significantly transform the field of medicine. The enhancement of therapeutic efficacy could increase the survival rate for patients with pancreatic cancer and pave the way for many other solid cancer treatments.

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