Perspective Article

The relation between T-cells and cancer treatment

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Cancer is one of the most fatal diseases in the world. Various therapies can treat the disease and currently, adoptive cell therapy is being researched as a more effective treatment rather than chemotherapy. Adoptive cell therapy is touted to cure cancer and is currently being researched and developed to treat several diseases like lymphoma, an unresponsive and recurring illness. After the discovery of CAR (Chimeric Antigen Receptor) T-cell therapy, a type of treatment in which a patient's T-cells are modified in the laboratory to attack cancer cells. This thesis explains the consideration to introduce T-cells in cancer treatment and points out its further application prospects. T-cells play a considerable role in the body's immune system, but is yet to be studied extensively to strengthen antigen specificity and mitigate the side effects of T-cell therapy.

Keywords: T-cells, cancer therapy, immune system, adoptive cell therapy, CAR T-cell, chemotherapy.

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Watch a video introduction by the authors at https://youtu.be/vaegKm8Jedc

Background

Definition of T-cells

Cancer is the second most lethal disease in the world, after heart disease. The mortality rate of cancer is increasing every year around the world due to an aging population. Despite the advancement in diagnostic and drug development, there are still many cancer patients with relapses and in advanced stages that do not respond positively to any standard treatments available. Most recently,many more cancer treatment options other than chemotherapy are available.. One of those modern cancer treatments is the use of adoptive cell therapy, especially CAR T-cell therapy. In the US, a clinical trial proved that CAR T-cell therapy has a success rate of 82% (Parameswaran & Nirav, 2020) compared to only 15-28% of chemotherapy success rates (Lillis, 2019).

T-cells are a component of white blood cells in the immune system and play a special and important role in antigen-specific immune responses. When a foreign antigens is detected, these cells identify and attack the virus-infected cells.

Function of T-cells

T-lymphocytes originate from hematopoietic stem cells that are produced in the bone marrow. Some of these

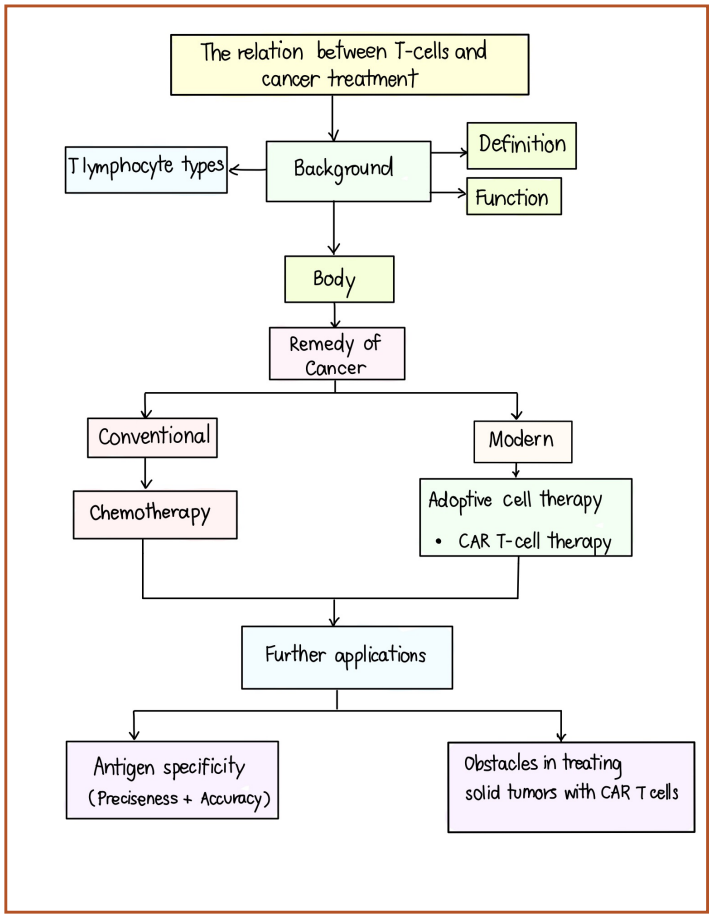

Figure 1. *The overview topics of the thesis.*

pluripotent cells will become lymphoid progenitor cells, which leave the bone marrow and travel through the blood to the thymus. They undergo a selection process in the thymus where the majority of developing T-cells (called thymocytes) do not survive. Thymocytes that have receptors to self-antigen molecules receive negative signals and are removed from the repertoire (TeachMe Physiology, 2021).Each T-lymphocyte will develop its own T-cell receptor (TCR) specific for a particular antigen. The T-lymphocytes that survive the thymus selection will mature and leave the thymus. They will circulate through the surrounding lymphatic organs, ready to encounter specific antigens and be activated. Once activated, T-cells will proliferate and differentiate into effector T-cells.

Figure 2 shows the hallmark of the cancer cell, highlighting the important details of a cancer cell. Unlike normal cells which normally regulate their size by controlling the number of cells during cell division, cancer cells can ignore signals that would normally stop them at cell dividing checkpoints in order to pass on their mutations. In addition, mutation in gene coding for proteins allows cancer cells to resist cell death. This

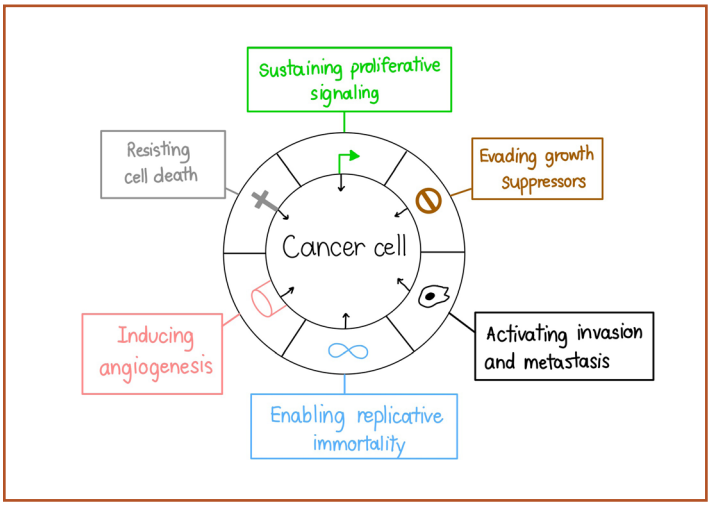

Figure 2. *The Hallmarks of cancer (Cell 2011)*

means they can develop into neoplasms or tumors as a result.

The CD8 co-receptor interacts with class I MHC (Major Histocompatibility Complex) with a low affinity that varies by genotype. Despite this, CD8 involvement can improve a T-cell's sensitivity to its homologous class I pepMHC complex. As a result, conventional wild-type affinity TCRs are adequate to deliver extraordinarily sensitive responses when targeting class I pepMHC. Because of the synergy with CD8, normal CD8 T-cells have been reported to respond to as few as one to three agonist pepMHC complexes on the cell surface. In the typical anti-tumor environment, CD8's capacity to synergize with even low affinity TCRs can be helpful, as most anti-self pepMHC reactive T-cells would have been eliminated in the thymus if they had even modest affinities.

Transforming CD4 T-cells with TCRs that have higher affinity against a class I MHC tumor antigen can result in CD4 T-cell responses against tumors. The engagement of the affinity-engineered TCR with one or more self-pepMHC complexes with affinities over the CD8-independent threshold appears to be the cause of CD4 T-cell activation. (Stone & Kranz,2013)

T Lymphocyte types

Cytotoxic T Lymphocyte

Also known as CD8+ cell, it is one of the types that kill their target cells primarily by releasing cytotoxic granules into the target cell. When classified by Major Histocompatibility Complex (MHC), these cells recognize their specific antigens, such as viral fragments I

molecules present on the surface of all nucleated cells (Figure 3A). MHC Class I molecules interact with a protein called CD8 on the cytotoxic T-cells. Cytotoxic T-cells need several signals from other cells to be activated, such as dendritic cells and T-helper cells. Their main function is to kill virally infected cells, but they also kill cells with intracellular bacteria or tumorous cells.

T-Helper Lymphocyte

T helper cells (Th) have a wider range of effector functions than CD8 T cells and can differentiate into many different subtypes, such as Th1, Th2, Th17 and regulatory T cells. (Figure 3B)

They become activated when they are presented with peptide antigens by MHC Class II molecules. These are shown on the surface of Antigen Presenting Cell (APC). MHC Class II molecules interact with a protein called CD4 on the T helper cells, which helps to identify this cell type.

The roles of a CD4 T cell may include activating other immune cells, releasing cytokines, and helping B lymphocytes to produce antibodies. They help to shape, activate, and regulate the adaptive immune response.

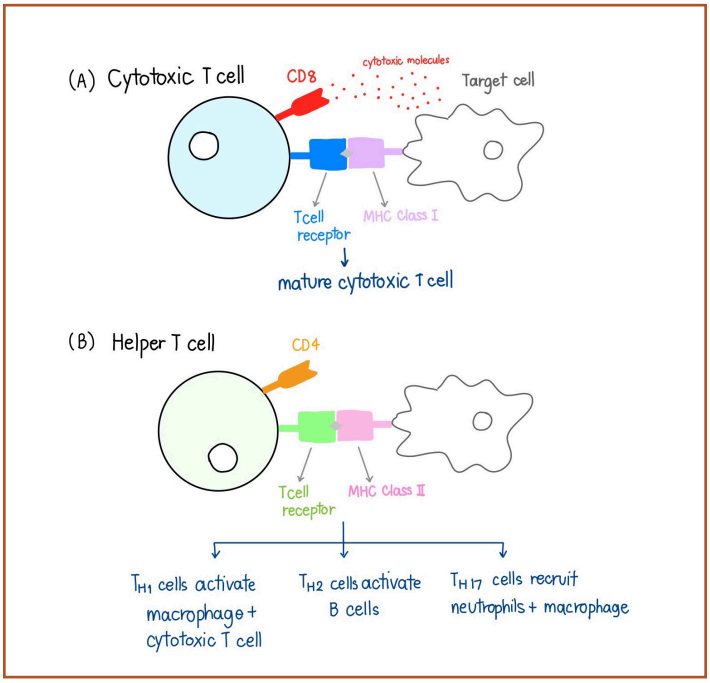

Figure 3. *Cytotoxic T cell and Helper T cell regulation*

Memory T Lymphocyte.

Memory T lymphocytes play an important role in the immune system because they can rapidly proliferate into a large number of effector T lymphocytes after re-exposure to antigen and have a low activation threshold. They provide the immune system with memory against previously encountered antigens. This means that if the same antigens re-enter the cell again later in the future, they can simultaneously kill them much faster and with more intensity. Memory T lymphocytes may either be CD4+ or CD8+.

Remedy for Cancer

Conventional Lymphoma Cancer Therapy

Many chemotherapy drugs are useful in treating lymphoma but usually used in combination with other drugs. The number of drugs, their doses, and the length of treatment depend on the type and stage of the lymphoma. Some of the drugs most commonly used to treat lymphoma (divided into groups based on how they work) are Alkylating agents, Corticosteroids, Platinum drugs, Purine analogs, Anti-metabolites, and Anthracyclines.

Sometimes, this treatment is effective in treating cancer by itself, but more often it is used in combination with:

- Surgery: A doctor removes cancerous tumors or tissue, or organs contaminated with cancerous cells.

- Radiation therapy: A doctor uses invisible radioactive particles to kill cancer cells. It may be delivered by a special machine that bombards parts of your body from the outside or by putting radioactive material on, near, and even inside the body.

Doctors give chemotherapy treatments in cycles, in which a period of treatment is followed by a period of rest to allow the body time to recover. Patients may have 3 weeks of recovery time before repeating the treatment. Each 3-week period is called a treatment cycle. Several cycles make up a chemotherapy course. A course usually lasts 3 months or more (Cancer. Net, 2019). Most chemotherapy treatments are given on an outpatient basis (in the doctor's office or clinic or hospital outpatient department), but some might require a hospital stay.

Modern Lymphoma Cancer Therapy

Adoptive Cell Therapy

Adoptive cell therapy involves the isolation and ex vivo expansion of tumor-specific T-cells to achieve a greater number of T-cells than can be obtained by vaccination alone. Tumor-specific T-cells are then injected into patients with cancer, allowing their immune system to predominate the rest of the tumor with T-cells which can attack and kill the cancer. There are many forms of adoptive T-cell therapy that can be used to treat cancer; culturing tumor infiltrating lymphocytes (TIL), isolating and expanding one particular T-cell or clone, and even using T-cells that have been engineered to potently recognize and attack tumors.The one we are specifically concerned with is CAR T-cell therapy due to its most advanced type of treatment (Cancer Vaccine Institute, n.d.).

CAR (Chimeric Antigen Receptor) T-cell therapy

This treatment employs a genetic engineered T-cell called "CAR-T-cell" i.e. the T-cell that expresses a hybrid T-cell receptor (TCR) molecule in which the outside part of TCR is replaced by a small fragment of antibody (Fernández, 2021). This chimeric receptor allows the T-cells to recognize a specific antigen on tumor cells. When the CAR-T cell binds its target, an intracellular signaling domain activates the T-cell to kill the target cell. (Watson, 2020) There are several generations of CARs, which carry additional internal domains that can further enhance the immune response against the programmed target.

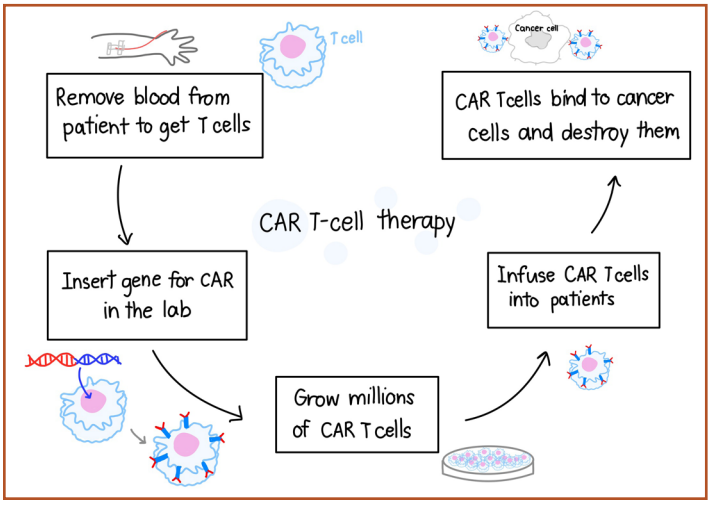

Figure 4. *CAR T-cell therapy (cancer 2020)*

The most common procedure for CAR-T cell therapy starts with the extraction of T-cells from the patient being treated, a process called leukapheresis (Figure 4). Growing theT-cells in the lab can take 2 to 8 weeks. During this time, the patient may receive chemotherapy and radiation therapy to kill a few other immune cells. Lowering immune cells makes the transferred T-cells more efficient. After these treatments, the T-cells grown in the lab will be given back to the patient intravenously. (National Cancer Institute, 2020).

Possible side effects

Chemotherapy

As with most drugs, Chemotherapy drugs may cause undesirable effects. These side effects depend on the type drugs, dosage given, and the duration of treatments. Common side effects include: hair loss, mouth sores, loss of appetite, nausea and vomiting, diarrhea or constipation, increased chance of infection (from a shortage of white blood cells), bleeding or bruising after minor cuts or injuries (from a shortage of platelets), and lastly, fatigue and shortness of breath (American Cancer Society, 2018).

If serious side effects occur, the dose may be reduced or treatment may be suspended.In some cases, the doctors might prescribe drugs to lessen these side effects. For example, drugs can be given to prevent or reduce nausea and vomiting (American Cancer Society, 2018).

Adoptive Cell Therapy

The most common side effects seen are:

- Cytokine release syndrome, which is similar to flu-like symptoms (headache, fever, chills, severe nausea, vomiting, diarrhea, severe muscle or joint pain), shortness of breath, low blood pressure and fast heart rate. These symptoms are mild in most patients but can be serious and life threatening (St. Jude Children's Research Hospital, 2019)

- Neurologic events can also be experienced and can be serious in some patients. Neurologic events include encephalopathy (brain disease, injury, malfunction), confusion, aphasia (difficulty understanding or speaking), drowsiness, agitation, seizures, loss of balance and altered consciousness.

- Low white blood cell count (Neutropenia)
- Low red blood cell count (Anemia)

Fortunately, most of the side effects can be managed with drugs, for example, tocilizumab (Actemra) and siltuximab (Sylvant) reduce the action of the cytokine or resolved on their own without the need for treatment depending on the patient's overall health (American Cancer Society, 2018).

Further applications

Chemotherapy serves the least effective treatment for cancer as it randomly targets the antigens or cells, which may eventually cause more fatal side effects. On the other hand, adoptive cell therapy, especially in CAR T-cell therapy, is preferred since it has considerably lower side effects and targets specific antigen. The treatment of advanced stage cancers and solid tumors are not yet fully practical although its efficacy has been demonstrated in mice (Ktori, 2021).

Hence, intensive studies of treatment should be encouraged to predict the possible applications of T-cells in the future. As listed below, the research team would be focusing on these main areas to be further researched in the CAR T-cell therapy (Ma et al., 2019)

Antigen specificity (Preciseness + Accuracy)

Multi-targeting CARs have several advantages over generic anonymous CAR molecules. By releasing cytokines and cytolysis in vitro and reducing the tumor burden in the body, the anticancer effects of CAR-T cells may be further enhanced. Other structures, such as tanCAR, may strengthen their function by altering their interaction with tumor antigens. However, the percentage of tumor cells targeting within the tumor tissue should be associated with a multi-target CAR. There is still a growing need to look for new antigens as potential targets.

Obstacles in treating solid tumors with CAR-T cells

CAR-T cells infiltrate into tumors. OnceCAR-T has been passed into the tumor, it goes through some processes (rolling, adhesion, expansion and chemical reaction) before attacking the tumor since solid tumors have a unique histopathological character. The same applies to tumor-related fibroblasts and myeloid cells that form an extracellular matrix. Although these properties support solid tumor growth, CAR-T infiltration difficulties can occur in the area tumor treatment.

CAR-T cells traffic to the tumor sites. To bind to a target protein on the tumor surface, CAR-T cells must first enter the tumor. In the case of solid tumors and unlike hematologic cancer, the captured T-cells that infiltrate the tumor site are often severely limited by the immune environment. It is also different from hematologic cancers in which CAR-T cells are easily targeted and accessible by certain chemicals secreted by solid tumors that prevent T-cells from entering and infiltrating the tumor lesion. Because there is no corresponding chemical receptor expressed on T-cells, it is difficult for CAR-T to traverse and infiltrate tumor regions which greatly impedes the ability of CAR-T cells to kill tumor cells. Hence, in order to overcome this barrier, T-cells must be modified to show chemoreceptors that match the chemokines obtained from tumors.

Reversal of the immunosuppressive microenvironment. Small immunocompromised environments within solid tumors have a histological effect represented by high-density blood vessels and widespread vascular leakage. These changes result in hypoxia, low pH, immune cells, increased inhibitory checkpoints, and more tumor-derived cytokines.

Next Steps

We hope that our research will be of great help to many researchers and students around the world in conducting experiments to find the best cancer treatment options.The further applications of this thesis is slightly far beyond the overall concepts in high school biology. As we are currently living in Thailand, our next step might be to contact a Thai or international oncologist (a doctor who specializes in diagnosing and treating cancer) for conducting experiments to learn more about the possible side effects of T-cell therapy.

Author Contributions

This study began with a simple idea of finding ways to help people who have cancer. The research team asked for a consultation after settling the topic. P.P. provided some concise and clear guidelines for brief concepts. A.A. and P.T. wrote the manuscript, interpreted data and the platform. A.A.and P.T. worked methodically and progressively after receiving instructions from P.P. A.A., P.T., and P.P. helped approve, read and fix the final

manuscript. This research paper was completed with the joint efforts of the team.

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