Cancer Immunology — Anticancer Therapies and Cancer Vaccines

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Recently, it has become clear that cancer and our immune system communicate with each other. Because of this, our immune system eventually allows cancer cells to go unchecked, and at a certain point, cancer cells ‘escape’ our immune system's response. With this understanding, more recent anti-cancer medications are targeting the different immune checkpoints that are known to fail in identification of cancer cells.

Introduction

Cancer immunology is defined as a complex interaction between cells of the immune system with cancerous cells.

Our immune system can identify cancer cells and is capable of getting rid of them until cancer cells develop some strategies to avoid this natural protective mechanism. These strategies include **immunoediting** and **immune checkpoint pathways**.

Immunoediting

Cancer cells can be classified into two types: the ones that express their unique **antigens** that can be recognized by immune T-cells, and others that do not

express the antigens. Our immune system can only identify the first type of cancer cells and by selectively eliminating them, it allows room for those cancer cells that do not express any identifiable surface antigens to T-cells to grow and proliferate. This process is known as **immunoediting**. It consists of three sequential phases: elimination, equilibrium, and escape.

- In **elimination** phase, the cancer cells having unique surface antigens are successfully eliminated by the innate and adaptive arms of the immune system.
- In **equilibrium** phase, after elimination of the major portion of cancerous cells, those sporadic tumor cells that do not express any identifiable antigens to our T-cells survive.
- In **escape** phase, the sporadic cancer cells having reduced immunogenicity grow and proliferate and have further acquired resistance to immune detection by making subtle genetic changes.

Immune Checkpoint Pathways

Some cancer cells produce molecules that **suppress the immune response**, and they grow in an environment that is suppressive to T-cells. This process is known as **immune checkpoint pathways**.

Possible Important Targets in the Immune Checkpoint Pathway

Several receptors have been identified that **suppress T-cells** against cancer cells. It is thought that cancer cells release possible molecules that **stimulate** these receptors, for instance, the cytotoxic T-lymphocyte-associated protein 4 (**CTLA-4**) and the programmed cell-death 1 (**PD1**).

When molecules secreted by the cancer cells attach to these receptors, the cytokine production is blocked and T cell response is suppressed. The cancer cells take advantage of this **immune checkpoint pathway** as a mechanism to avoid immune cells and hence proliferate excessively.

It was suggested that blocking these receptors on T-cells or engineered T-cells that do not express them will make it possible for the T-cells to escape the immune checkpoints. The therapies using these mechanisms have shown positive results, which are discussed below. Engineered T-cells have been recently used in **acute lymphoblastic leukemia**.

Anticancer Therapies and the Immune Checkpoint Pathway

Our current understanding of the **CTLA-4 pathway** answers why tumor cells escape our immune system. The CTLA-4 pathway is also involved in regulating our immune response against **autoimmunity** and **infections**. Cancer cells hijack the CTLA-4 pathway and make our immune cells—especially cytotoxic T-cells—fail to recognize them as foreign cells. Thus, the tumor cells grow unchecked and eventually escape our immune response.

The first trials with anti-CTLA-4 antibodies were started ten years ago. Patients with **melanoma** were prescribed anti-CTLA-4 medications, and the results were very

encouraging. Tumors' invasiveness, **metastasis**, and overall survival improved after the introduction of anti-CTLA-4 treatment. Eventually, the FDA approved **ipilimumab. an anti-CTLA-4 antibody**, for melanoma.

Anti-PD-1 antibodies such as **pembrolizumab** and **nivolumab** have been undergoing extensive trials in diverse cancers including non-small-cell lung carcinoma, renal cell carcinoma, bladder cancer, lymphoma, and melanoma. In 2011, the FDA approved pembrolizumab for melanoma, and in 2015 they approved nivolumab for non-small-cell lung carcinoma.

In 2014, it was found that the PD-1 and the CTLA-4 pathways inhibit cytotoxic T-cells in two different and non-overlapping pathways. Thus, it was suggested to combine anti-PD-1 and anti-CTLA-4 treatments looking for possible **synergetic effects**. Currently, a phase I clinical trial is testing the efficacy of anti-PD-1 plus anti-CTLA-4 combined therapy versus monotherapy in advanced melanoma, and the preliminary results confirm the presence of a synergetic effect.

Who Will Respond to Immunotherapy Targeting the Immune Checkpoint Pathway?

Unfortunately, a significant number of cancer patients do not respond to anti-CTLA-4 or anti-PD-1 therapy. It was suggested that good responders usually have high expression of the PD-1 legend, which is responsible for inhibiting the cytotoxic T-cells via the PD-1 pathway. Therefore, patients with low PD-1 legend levels are not good candidates for anti-PD-1 therapy.

Adoptive Cell Transfer as Immunotherapy in Cancer

Patients with tumors that are highly infiltrated by lymphocytes might benefit from adoptive cell transfer techniques. **Tumor infiltrating lymphocytes (TIL)** are known to be able to destroy the tumor if they are promptly activated and are in enough numbers.

Adoptive cell transfer helps with the second problem by isolating and expanding TILs and then reinfusing the expanded autologous lymphocytes back to the blood. Immunotherapy by anti-PD-1 and anti-CTLA-4 is responsible for promptly reactivating TILs.

Patients with specific forms of immune cancers, such as B-cell malignancies, including **multiple myeloma,** are possible candidates for **engineered T-cell therapy**. Engineered T-cells can express tumor specific antigen receptors or CAR receptors. They have been used in melanoma, with little success.

Patients with **acute lymphoblastic leukemia**, **chronic lymphocytic leukemia**, **neuroblastoma**, and **glioblastoma** have shown excellent response to CAR+ engineered T-cells with remission rates of up to 90 % in acute lymphoblastic leukemia.

Cancer Vaccines

Cancer cells are known to share certain antigens which can be used to induce immunity against them. The Wilms-tumor-1 antigen is shared by acute myelogenous leukemia and breast cancer. Vaccination with Wilms-tumor-1 antigen might lead to tumor regression.

Another example is the anaplastic lymphoma kinase antigen, which is shared by anaplastic large cell lung and non-small-cell lung carcinoma, in addition to neuroblastoma. This antigen was also used as a vaccine in secondary prevention of these tumors with good results.

The best results of cancer vaccines can be achieved when **combined with other forms of immunotherapy or chemotherapeutics**. Unfortunately, primary prevention of cancer by cancer vaccines is yet to be tried in humans, despite several studies in animals.

Prophylactic	Therapeutic
• Virus-associated tumors • Liver cancer: hepatitis B virus • Cervical cancer: human papilloma viruses – gardasil (HPV 6, 11, 16 and 18), cervarix (HPV 16 and 18)	• Tumor antigens – in most cases aim is primarily to induce specific cytotoxic T-cell responses, but sometimes antibody also desirable • Provenge – prostate cancer vaccine using patient´s own cells

Human papilloma virus is known to be the most common cause of **cervical and vaginal carcinoma**. Human papilloma virus vaccines dramatically decreased the incidence of these cancers, but such vaccines are not cancer vaccines per our definition. Cancer vaccines should use an antigen that is known to be expressed by certain tumors to elicit an immune response.

References

Voena C, Chiarle R. Advances in cancer immunology and cancer immunotherapy. Discovery Medicine. 2016. 21(114):125-33. PubMed PMID: 27011048. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27011048

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