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Introductory Chapter: Are We There Yet? The Long and Winding Road to Cancer Immunotherapy

Hilal Arnouk and Sana Moqheet

1. History of cancer immunotherapy

Cancer immunotherapy has become an innovative approach that both pushes the medical and scientific community to better understand our own immune system and charts a new frontier in the fight against one of the leading killers in the world, cancer. The advent of this line of work dates back to the discovery of vaccine. Luminary scientists in the nineteenth century such as Joseph Lister, Louis Pasteur, Robert Koch, and most notably William Coley have allowed for a better understanding of the immune responses and the establishment of vaccines, including vaccines directed against malignant tumors [1–4].

While the basic concept of using immunotherapy to combat cancer was practiced in the scientific community, specifically by Coley, scientists Thomas and Burney were the first to propose the theory of cancer immunosurveillance in 1957. The premise behind their theory was that lymphocytes, an integral part of the immune system, have the capability to eliminate the mutated cancerous cells throughout the human body [5–8]. However, due to a lack of scientific proof-of-concept and the inability to culture the lymphocytes *ex vivo* for extended periods of time, the next development did not occur until a few decades later. From the 1970s onward, the scientific community has discovered the utility of several different immune therapies to treat cancer including interferon alpha (IFN- α) [9], the T cell growth factor interleukin 2 (IL-2), monoclonal antibodies targeting tumor-associated antigens, and the first FDA-approved cell-based cancer vaccine developed for patients with advanced prostate cancer in 2010 (**Figure 1**).

This chapter will give a brief overview of few of these therapies that scientists and physicians are currently utilizing in the fight against cancer.

2. Tumor antigens

Tumor cells are distinguished from normal cells in a tissue by the presence of unique proteins known as tumor antigens. They can be further divided into two broad categories, tumor-associated antigens and tumor-specific antigens.

Tumor-associated antigens can arise from oncofetal genes that become aberrantly expressed in malignant cells, such as alpha-fetoprotein (AFP) in liver cancer and the melanoma-specific antigens of the MAGE family [10], or from cancer-testis antigens that are expressed normally in the germ cells and become activated in cancers, such as the New York esophageal squamous cell carcinoma 1 (NY-ESO-1) antigen [11]. Tumor-associated antigens also include tissue

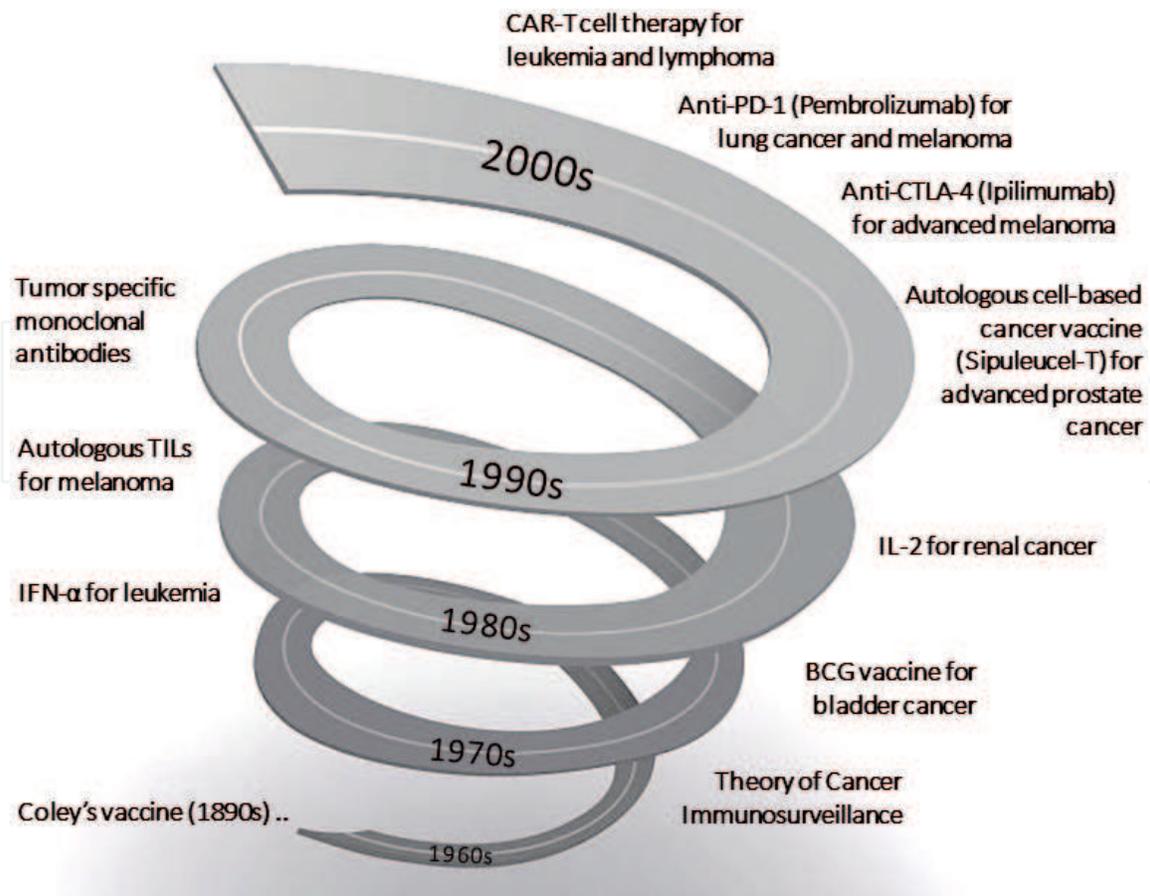


Figure 1.
Key events in the history of cancer immunotherapy.

differentiation antigens, such as tyrosinase in melanoma [12], and viral antigens in a number of malignancies where viral oncogenesis is implicated, such as HPV E6 and E7 oncoproteins in HPV-associated cervical cancers [13]. On the other hand, tumor-specific antigens are usually the products of mutated oncogenes or tumor suppressor genes, such as *ras* and *p53*.

3. Cancer vaccines

While it is well established that vaccines are a way to stimulate the immune system against infectious agents, the concept of harnessing the power of a vaccine to eliminate cancers remains revolutionary. Cancer vaccines work through inducing a specific antitumor T cell response.

Cancer vaccines are divided into prophylactic and therapeutic vaccines. For instance, a prophylactic vaccine against human papillomavirus (HPV) can prevent several cancer types caused by virus, such as cervical cancer and some cancers of the oropharynx [14, 15], and hepatitis B virus (HBV) vaccine provides protection against liver cancers initiated by the hepatitis B virus [16]. Alternatively, therapeutic cancer vaccines trigger an immune response against an existing tumor by inducing T cell response within the tumor microenvironment. Various formats have been developed for therapeutic cancer vaccines, including peptide fragments and full-length tumor antigens, vectors for genetically encoded tumor antigens, whole tumor cell contents, and autologous dendritic cell (DC) vaccines. Most notably, Sipuleucel-T (Provenge) was the first FDA-approved cell-based cancer vaccine developed for patients with hormone-refractory prostate cancer and has shown to prolong the life of affected patients by several months [17, 18].

Since most tumor-associated antigens are not highly immunogenic on their own, an immune adjuvant is typically added to vaccine formulas. Examples of vaccine adjuvants include recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) and heat shock proteins [19–21].

4. Adoptive cellular immunotherapy

Adoptive cellular immunotherapy (ACT) is the process of transferring effector immune cells, such as T lymphocytes, to cancer patients, including modifying and expanding these immune cells *ex vivo* to target specific cancer cells [22, 23]. The transferred immune cells can have autologous or allogeneic origin. Two major approaches have been utilized for adoptive cellular immunotherapy, tumor-infiltrating lymphocytes (TILs) and chimeric antigen receptor-modified T cell (CAR-T) therapy.

4.1 Tumor-infiltrating lymphocytes (TILs)

A tumor-infiltrating lymphocyte is an immune cell that has moved into a tumor in the attempt to destroy the cancer. In this therapy, TILs are extracted from tumor tissue biopsies and cultured *in vitro* with IL-2 to expand the tumor-reactive clones. Once activated, lymphocytes are infused back into the patient [24].

4.2 Chimeric antigen receptor-modified T cell (CAR-T) therapy

Chimeric antigen receptor-modified T cell (CAR-T) therapy has emerged as a successful method in the fight against cancer, especially B cell hematologic malignancies [25]. This success lies within the chimeric antigen receptors (CAR) composed of single-chain variable fragment (scFv) and the costimulatory signaling molecules that can stimulate T cells and allow for direct antigen binding and activation, bypassing the requirement for antigen presentation by antigen-presenting cells (APCs).

CAR-T cell therapy has been especially effective against certain types of lymphoma and leukemia, such as refractory B cell lymphoma and acute lymphoblastic leukemia (ALL) [26, 27]. CAR-T cell therapy is a multistep process. First, patients are evaluated to determine if CAR-T cell therapy is an appropriate treatment. Second, T cells are isolated from blood. The patient's T cells are then taken into the laboratory to be genetically modified to express the chimeric antigen receptors (CARs) on their surfaces. As discussed above, these essential receptors allow for the modified T cells to recognize tumor antigens. Finally, the CAR-T cells are infused back into the patient, and a recovery period of 2–3 months is expected [28].

Overall, CAR-T cell therapy has become a leading area of continued growth and research in the field of cancer immunotherapy. It has had much success in both pre-clinical and clinical applications, and the next steps involve harnessing the power of modified T cells to aid in eliminating solid tumors including aggressive cancers, such as sarcomas.

4.3 NK cell therapy

Natural killer (NK) cells are large granular lymphocytes that can destroy cells organically, without the requirement for priming first. One of the major hypotheses related to NK cells is the “missing self” hypothesis, which states that NK cells have the ability to destroy cells that do not display major histocompatibility complex

(MHC) class I molecules [29]. Given the extraordinary functions of NK cells in recognizing and destroying altered cells, NK cell-based therapies have become a wide area of research for diseases like cancer. One such targeted therapy is the use of NK alloreactivity, specifically in acute leukemia and other types of hematologic cancers. MHC class I inhibitory receptors, specifically killer immunoglobulin-like receptors (KIRs), have been utilized to exert NK cell alloreactivities as a way to combat leukemic cells [30].

5. Antibody-based treatments

Antibodies are arguably one of the most important aspects of the human immune system. They serve to bind to antigens and allow for flagging of cells with specific antigens for eradication. An antitumor monoclonal antibody is a genetically engineered immunoglobulin that is produced to recognize a specific tumor antigen on the surface of a cancer cell [31].

Monoclonal antibodies work in a multitude of ways including flagging cancer cells, blocking growth of cells, blocking immune inhibitors, directly attacking cancer cells, and bridging cancer and immune cells [32]. Monoclonal antibodies come in two different varieties, naked and conjugated. Naked monoclonal antibodies work individually and can attach themselves to antigens on cancer cells. For instance, trastuzumab (Herceptin) can bind to HER2 oncogene/tumor antigen that is overexpressed in a subset of breast cancers, which blocks the growth and proliferation of the malignant cells [33]. Conjugated monoclonal antibodies work by carrying a radioactive or cytotoxic drug into proximity to the tumor cells, thus killing these malignant cells [34, 35]. As with other cancer immunotherapies, antibody-based treatments carry the risk of adverse side effects that include fever, weakness, nausea, and rashes.

6. Immune checkpoint inhibitors

Immune checkpoint inhibitors are inhibitory molecules on immune cells that prevent the immune system from attacking the organism's own tissues. Two of the identified immune checkpoints are programmed cell death-1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [36].

Interaction of PD-1 and its ligand PDL-1 leads to T lymphocytes' dysfunction and exhaustion. PDL-1 is shown to be highly expressed on cancer cells [37]. Consequently, the blockage of PD-1 and PDL-1 interactions using immune checkpoint inhibitors allows tumor-specific T lymphocytes to exert their function by recognizing and destroying cancer cells. Nivolumab and pembrolizumab are monoclonal antibodies that function as PD-1 blockers and are being currently being used to treat patients with advanced melanoma and non-small cell lung cancer [38, 39]. Similarly, CTLA-4 inhibits T cell activation. Thus, CTLA-4 blockage with inhibitors, such as ipilimumab, enhances the immune responses against malignant tumors such as melanoma [40].

It is important to note, however, that the use of immune checkpoint inhibitors in cancer immunotherapy is frequently followed by inflammatory and autoimmune side effects that include endocrine effects, rash, and hepatitis [41, 42].

In conclusion, cancer immunotherapy remains a field that has tremendously changed our understanding of how to best treat cancers. While advancements have been made, there are many more discoveries to be made as the field of tumor immunology is growing exponentially.

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