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Cancer and the Immune System: The History and Background of Immunotherapy

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ABSTRACT

Objective: This article will outline the link between the immune system and cancer, and provide a historical timeline of immunotherapy developmental milestones.
Data Sources: Published data and peer reviewed publications/manuscripts, and textbook chapters.
Conclusion: Science has provided a greater understanding of the interactions between cancer and the human immune system. As this knowledge has grown, there has been significant progress in the development of clinically effective cancer immunotherapies.
Implications for Nursing Practice: Nurses' knowledge of the different types of immunity and the interaction of cancer cells with the immune system provides foundational knowledge for understanding cancer immunotherapy. Familiarity with the history of cancer immunotherapy will allow nurses to better comprehend why immunotherapy is now a pillar of cancer treatment that continues to develop. This knowledge will translate to better understanding and provision of care for patients receiving immunotherapy for the treatment of cancer.

Introduction

The human immune system is responsible for recognizing self versus non-self, thereby protecting the body from diseases of exogenous and endogenous origins. Composed of white blood cells and organs and tissues of the lymph system, including thymus, spleen, tonsils, lymph nodes, lymph vessels, and bone marrow, the immune system identifies numerous threats and eliminates them to continue homeostasis. To understand how immunotherapy has become a pillar of cancer therapy, an understanding of cancer cells and immune system interaction is needed. Different from chemotherapy, which kills cancer via cytotoxic properties, immunotherapies – while there are various types with different mechanism of action – overall use the host immune system to kill tumor cells. This article will review this interaction and will additionally provide a historical review of immunotherapy developmental milestones to appreciate the current use of immunotherapy to fight cancer.

The Beginnings of Cancer Immunotherapy

In 2013 the journal *Science* declared immunotherapy for the treatment of cancer the "Breakthrough of the Year."[1] Yet, immunotherapy for the treatment of cancer and other diseases predates the 2013 declaration by over a century. Edward Jenner, who developed the first successful vaccine, the smallpox vaccine, in 1796, is generally considered to have laid the foundation of immunology with this development.[2,3] In 1891 Dr William Coley, now considered to be the "Father of Immunotherapy," began to search for a more effective method than surgery to treat sarcoma after the painful death of an 18-year-old patient.[4]

The impact of this experience led Dr Coley to perform a case review where he discovered several cases of patients with a diagnosis of sarcoma that developed erysipelas caused by *Streptococcus pyrogenes* whose sarcoma either went into spontaneous long-term remission or who disease had disappeared. Later in 1891, Dr Coley began injecting patients' tumors with "Coley's mixed toxin," a mixture of live and inactivated *Streptococcus pyogenes* and *Serratia marcescens*.[5] He was able to achieve responses including durable and complete remission for patients with various malignancies including sarcoma, lymphoma, and testicular cancer.[6] Despite these responses, there was not a great understanding of the mechanism of action of these "toxins" and purposefully infecting patients with pathogenic bacteria caused concern amongst oncologists.[7,8] As such, other treatment modalities including surgery, radiation, and chemotherapy became the mainstay of cancer therapy until decades later.

Understanding the Immune System

The immune system is generally divided into two facets, innate and acquired or adaptive immunity, which together perform immune

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Table 1
Innate and adaptive/acquired immunity.

	Innate	Adapative/Acquired
Specificity	• Nonspecific • Present at all times • Reacts to all foreign pathogens	• Specific • Requires activation • Direct response to triggering pathogen
Response time	• Immediate reaction • General defense	• Delayed reaction • Specific defense
Memory	• Absent ◦ Same response with repeated exposure to same pathogens	• Present ◦ Antibody development ◦ Provides retained immunity to repeated exposure to same pathogens
Cell components	• Macrophages • Dendritic cells • Phagocytes • Neutrophils • Natural killer cells	• T lymphocytes • B lymphocytes

surveillance, distinguishing self from non-self (Table 1). The inherent distinction between self and non-self occurs at a biochemical level, including DNA composition and glycoprotein structure on cells. Even the minutest antigen (non-self) can be detected and attacked via the immune response. This division is a simplification because the two types of immunity often have overlapping roles and are closely related.

Innate immunity is present from birth and activates a non-specific immune response with cytokine release in the presence of non-self materials. Comprised of physical barriers including skin and mucous membranes, physiologic barriers including temperature and pH, and more intricate, but still non-specific parts including neutrophils, mast and dendritic cells, and macrophages, this is the body's first line of defense. Innate immune responses are rapid and occur independently of antigens.[3,9] Cytokines are a central player in innate immunity and mediate several immune functions. Together, the pieces of the non-specific innate immune system mount a generalized immune response to eliminate antigens.[9–11] If this response is not sufficient, a more specific response is mounted by the adaptive or acquired immune system.

Adaptive or acquired immunity, in contrast to innate immunity, is specific and time-dependent, adjusting to diverse stimuli and develops over time via exposure to non-self materials. Adaptive immunity encompasses B-cell antibody production and action of antigen-presenting cells to helper T cells, which stimulate cytotoxic T cells. Cytotoxic T cells target markers on non-self cells to eliminate the non-self matter. The final step in the adaptive immune response is formation of immune memory. This process takes place through four steps, starting with specificity, which denotes that distinctive antigens trigger specific response to a specific antigen.[3,9] The second step is trafficking, which describes the process of activated immune cells migrating to specific target sites in the body. Adaptability follows, allowing for additional immune response by antigen spreading. In reference to cancer, when a tumor-specific T cell is stimulated to start lysis of tumor cells, cell fragments and antigens are picked up by antigen-presenting cells and the immune system is activated. The central feature of adaptive immunity versus innate immunity is the development of immunological memory. This memory allows the immune system to recognize an antigen to which it has been previously exposed and leads to a more rapid and vigorous immune response upon re-exposure.

Together, these types of immunity provide defense against non-self substances, like bacteria, that enter our body. Because cancer is made of "self" cells and tissues, how then can the immune system be expected to recognize, fight, and ultimately destroy malignant cells? This is because cancer cells can be differentiated from "normal" self cells by their different biochemical make-up and antigenic structure and biologic behavior.[3,9,12] So how then do cancer cells evade the immune system and grow unchecked until they become detrimental to one's health?

Cancer Immunoediting: Immunosurveillance, Equilibrium, and Escape

Genes control growth, maturation, and death of normal body cells. Approximately 20,000 DNA-damaging events happen to each cell each day, which are regularly repaired by DNA repair pathways.[12,13] In cases when cells are not needed and/or become a threat, apoptosis or programmed cell death occurs to prevent proliferation of these cells. The hallmark of cancer cells is uncontrolled proliferation of mutated or abnormal cells that spread through the body and invade healthy tissue.[14,15] Cancer development and progression occurs via eight processes, sustained proliferation, evasion of growth suppressors, cell death resistance, replicative immortality, angiogenesis, metastasis, reprogrammed metabolism, and finally evasion of immune destruction.[9,13,14] Evasion of immune destruction has been studied for decades.

In 1909, Paul Erlich developed a hypothesis that tumors may be controlled by the immune system.[16,17] In 1957, Thomas and Burnet first proposed the theory of cancer immunosurveillance, which suggested that lymphocytes act as guards responsible for identifying and eliminating cells that have undergone mutations and differ from normal host cells.[16,18] Evidence and technology to conduct studies to generate supporting evidence was lacking in 1957, and so again there was a delay in examining this link between cancer cells and the immune system. Studies looking at the incidence of cancer in patients with immune suppression related to disease, such as HIV and AIDS, or post allogeneic transplant patients on chronic immune suppression therapy provided evidence to support the existence and importance of immunosurveillance.[17] From the mid-1970s through the 1980s there was again a research movement looking at cancer immunosurveillance.[19] Natural killer (NK) cells discovered at that time generated excitement until scientists could not develop an exact definition and comprehension of NK cells.[19] Today, it is known that cancer cells can be and are recognized by the immune system because of biochemical differences in cancer cells from normal self cells. There is a dynamic period, immunoediting, in which immune cells initially destroy tumor cells and eventually a time when the cancer cells through various mechanisms can evade immune system elimination.[17] *Immunoediting* is the current term, because it is inclusive of all phases of cancer and immune system interaction beyond immunosurveillance.[19]

The immunoediting hypothesis is composed of three phases (Fig. 1). The first phase is elimination and refers to a time when active immunosurveillance is ongoing. Cells not normally repaired by the inherent genetic DNA repair mechanisms that become malignant or potentially malignant can be initially identified and killed by the immune system via immunosurveillance.[3,9,13] Innate immunity followed by presentation to tumor antigens, dendritic cells, and then development to tumor specific CD4+ and CD8+ T cells allows for destruction of cancer cells. Immunosurveillance is widely considered to be the phase of undetectable and early tumor development.[13]

Following elimination is the second phase, equilibrium, during which tumor cells not destroyed by the immune system during elimination are still not destroyed, but are unable to progress. Tumor cells continue to coexist with the immune system. This is thought to be the longest of the three phases and theoretically could last for years.[9] The third phase of immunoediting is escape or evasion.

During the escape phase, cancer cells can grow and metastasize because of lack of control and elimination by the immune system. Generally, during scape the immune system becomes overwhelmed and can no longer contain the growth of malignant cells. Multiple

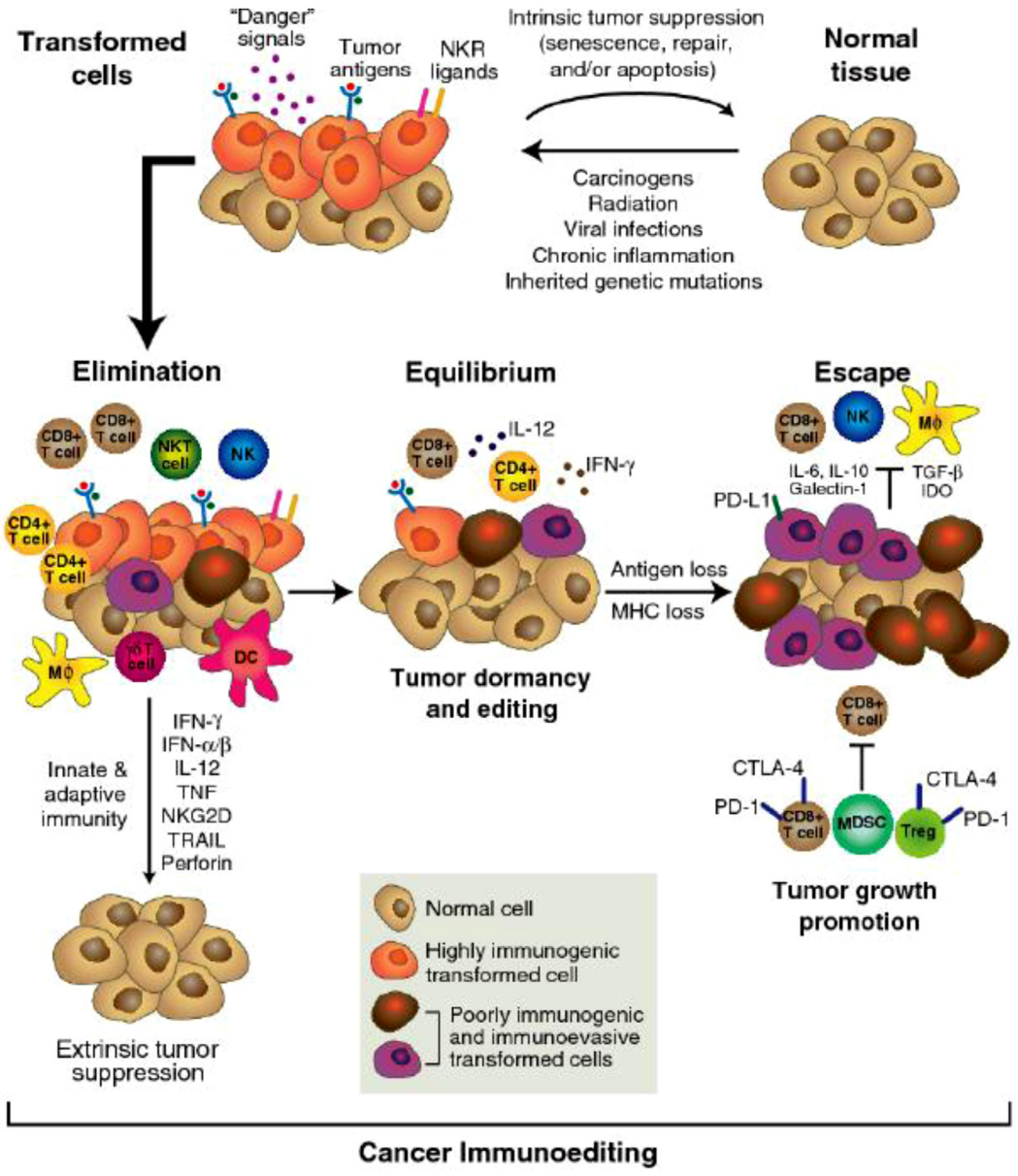

Fig. 1. Cancer Surveillance and Immunoediting. (Reprinted with permission from Schreiber, Old, and Smyth. *Science* 2011;331:1565-1570.[35]).

mechanisms allow malignant cells to evade elimination by the immune system, including suppression of the immune system by the tumor cell itself or by genetic acquisitions that allow immune suppression.[13,15,17] One such mechanism is the ability to express immune checkpoint molecules on the cancer cell surface, like those found on normal cells, and thus suppress the T cells at immune checkpoints and evade the immune system attack.[9,13,15] This ability to evade immune attack is again considered to be one of the hallmarks of cancer pathogenesis. So then how does immunotherapy treat cancer?

Fundamentals of Immunotherapy

Immunotherapy is defined as the use of materials that augment and/or reestablish the immune system's ability to prevent and fight disease.[9,20] A goal of immunotherapy is to balance the immune system to eliminate cancer cells while not producing unchecked autoimmune inflammatory responses that result in therapeutic limitations of immunotherapies.[15] Innate immunity is limited to release of cytokines that recruit immune cells to begin the non-specific immune response. The adaptive immune system plays a much more significant role in immune response to cancer cells because of the ability to specifically target non-self antigens.[9,15]

Resulting from this understanding, there have been various methods of immune therapy developed, including but not limited to vaccinations, monoclonal antibodies, and checkpoint inhibitors. Each immunotherapy seeks to increase immune function and differs by various mechanisms of action by which they are categorized. Immunotherapies are generally divided into active and passive immunotherapies. Active immunotherapy is the direct stimulation of an immune response, immune memory, and lasting response.[9] Oncolytic vaccines are an example of active immunotherapies. Passive immunotherapies, which include monoclonal antibodies, produce specific but often short-lived responses that therefore require regular administration of these treatments. Finally, there can be a delay in clinical and radiologic response to immunotherapy. This is because of the time it takes for an immune response to occur and followed by the time it takes for the T cells to destroy the tumor. Again, because of immune memory properties, there are benefits of immune therapy that include sustained immune action after cessation of therapy,

which may lead to continued antitumor effects and sustained overall survival.[9] There is some evidence that tumors that initially respond to immune therapy may become resistant over time. Trials to develop therapies to combat immunotherapy resistance are ongoing.[8]

Timeline and Types of Immunotherapy Development

Toxins and tumor necrosis factor

In the 1930s and 1940s until the early 1960s bacteria was again used with intermittent success to treat tumors by causing necrosis.[21] Tumor necrosis factor (TNF), also identified as a cancer immunotherapy in the 1970s, was thought be a major development in cancer therapy. Unfortunately, systemic infusion of TNF caused severe toxicities including fever, rigors, and pulmonary edema, and therefore was severely limited in its use and has since fallen out of favor in lieu of other available therapies.[22]

Vaccines

Oncolytic vaccines were first used in the 1920s, but after fatalities caused by the administration of the bacillus Calmette-Guerin (BCG) vaccine in the 1930,s this treatment was shelved until 1976. In 1976, Dr Alvaro Morales provided evidence that BCG could be used effectively and safely to treat superficial bladder cancer.[23] In 1990, the US Food and Drug Administration (FDA) approved the use of BCG vaccine for the treatment of superficial bladder cancer. Until 1990, clinically effective oncolytic vaccines remained intangible. The FDA approved the first cancer vaccine, sipuleucel-T, for castrate-resistant prostate cancer to extend overall survival of patients.[3] Limitations of cancer vaccines have been the lack of understanding on how to immunize patients to achieve cytotoxic T-cell response as well as circumvent and/or incapcitate tumor microenvironment to achieve anti-tumor response. Clinically relevant tumor death before they can occur.[15]

Interleukin 2

Interleukin 2 (IL-2) was first identified in 1976. High doses of IL-2 demonstrated clinical efficacy when administered to patients with established metastatic cancers by enhancing T-cell production. IL-2 as an immunotherapeutic was eventually approved by the FDA in 1991 for the treatment of metastatic kidney cancer and then for metastatic melanoma in 1998. Because of significant treatment toxicity and newer therapeutic developments, IL-2 therapy has fallen out of favor.[13]

Antibody therapies

The 1970s marked the development and production of monoclonal antibodies in the laboratory. Not until 1997 did continued research lead to the FDA approval of a clinically relevant monoclonal antibody, rituximab, for the treatment of non-Hodgkin's lymphoma.[24] Rituximab works by binding to CD20 on the surface of immature B cells and marks them for eradication by NK cells. Since that time more than a dozen additional monoclonal antibodies have been approved to treat many cancers, including but not limited to Hodgkin lymphoma, and colorectal, lung, and breast cancers.

Checkpoint inhibitors

The discovery of a singular protein on a cell called *cytotoxic T lymphocyte antigen 4* (CTLA-4) by a group of French researchers in the 1980s led to a revolution in cancer immune therapy and the evolution of immune checkpoint inhibitors. Dr James Allison discovered that CTLA-4 acted as a brake on the immune system by stopping T cells from mounting a full immune response.[25] He hypothesized that by blocking CTLA-4 molecules, the immune system brake would be removed and the T cells would be able to attack and kill the cancer cells. In 1996, Dr Allison published evidence that demonstrated this phenomenon in mice.[25] In 2010, Bristol-Meyers Squibb, who had acquired the CTLA-4 inhibitor, produced evidence that patients with metastatic melanoma receiving CTLA-4 checkpoint inhibitor lived 10 months compared with 6 months for patients who had not received the drug.[13] In 2011, ipilimumab, a CTLA-4 checkpoint inhibitor, received FDA approval for the treatment of metastatic melanoma.

In the 1990s Dr Drew Pardoll was able to obtain funding to test programmed death-1 (PD-1) and its ligand PD-L1, which had been discovered in Japan and identified as another brake on the immune system and T cells. Since that time, PD-1 and PD-L1 therapy have been approved by the FDA for the treatment of melanoma and lung cancers, to name a few. PD-L1 therapy has been approved for frontline therapy for lung cancer patients who have PD-L high (>50%) expression.[12] Studies related to checkpoint inhibitors used in combination with other checkpoint inhibitors or other treatment modalities (eg, radiation) are ongoing.

Oncolytic virus therapy

Theories about viruses as a method of treating cancer have been in circulation since the early 1900s. First were patients experiencing tumor regression after naturally occurring viral illness. This was followed by the targeted use of the rabies virus for treatment of cervical cancer in 1912.[26] Oncolytic viruses are defined as genetically modified or naturally occurring viruses that selectively replicate inside of and kill cancer cells without destruction of healthy/normal tissue.[27] While there are over 3,000 virus species, many cannot be used for cancer therapy. For a virus to be used, it needs to be nonpathogenic, must have cancer-selective killing activity, and the ability to be genetically modified to cause cancer cell death.[28] The year 1991 marked a milestone for oncolytic viral therapy when Martuza et al[29] were able to demonstrate that herpes simplex virus-1 (HSV-1) was able to be engineered to replicate selectively and target cells in brain tumors. Since that time, approvals first in China in 2005 for treatment of head and neck cancers was followed by the FDA approval of the first oncolytic virus therapy in the US. Talimogene laherparepvec (T-VEC) was approved in 2015 by the FDA for the treatment of melanoma and was subsequently approved in 2016 in Europe and then Australia.[26] The limiting factors have been toxicities and efficacy, because circulating antibodies may decrease effectiveness of the therapy as a whole. Currently, there are multiple oncolytic viral trials that are ongoing in the US and across the globe to establish more effective oncolytic viral therapy and create a wider use base for this type of cancer treatment.

Chimeric antigen receptor (CAR) T-cell therapy

Early in the 2000s T cells were studied to develop novel therapies, including the development of chimeric antigen receptor (CAR) T cells.[30] Patients with B-cell lymphomas who were exposed to genetically modified T cells experienced clinical responses. Even more significant outcomes (durable responses) occurred in patients with a history of chronic lymphocytic leukemia who were treated with genetically engineered T cells.[31,32] The year 2013 marks a significant milestone in the history of cancer immunotherapy with the results of CAR T-cell therapy clinical trials producing remarkable results. Outcomes data showed therapeutic efficacy with response rates around 90% for patients with B-cell acute lymphoblastic leukemia (ALL), children with ALL, and patients with aggressive non-Hodgkin's lymphoma.[33,34] These results were the basis for the 2017 FDA approval of tisagenlecleucel (CAR T-cell therapy). This was the first CAR T-cell therapy approved by the FDA and was approved for the treatment of pre−B-cell ALL in patients 25 years or younger.

Conclusion

Since 1891 there have been significant discoveries and success in using immunotherapy to prevent and treat cancer. Immunotherapy has become a pillar of cancer therapy, along with chemotherapy, surgery, radiation, and targeted therapies. Studies to prevent and combat immunotherapy resistance, to determine how to make a tumor "immune hot" so that there is better response to immunotherapy, and immunotherapy in combination with other immune therapies or other treatment modalities are ongoing. Immunotherapy is not yet a cure-all for cancer because not all tumors respond and not all patients survive, but there is promise for further development and efficacy in the future.

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