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Imagine training the body to attack cancer. As defined by the National Cancer Institute, cancer is a process by which abnormal cells divide without control and are able to invade other tissues.[1] This complex process is governed by genetic mutation, which results in cancer cells losing their resemblance to the normal cells they are ultimately derived from, overcoming built-in cellular mechanisms to prevent runaway growth, inducing neoangiogenesis or the formation of new blood vessels, as well as eventual metastasizing to foreign tissue sites.[1] Importantly, cancers develop an ability to evade the body's immune system through a variety of mechanisms, such as changing surface proteins that immune cells normally use to home in on foreign cells, accumulation of regulatory T-cells (Treg) that suppress the immune response, as well as secretion of specific immune signaling cytokines (e.g., interleukin 6 [IL-6] and 10 [IL-10]) to inhibit lymphocytes that normally kill tumor cells.[2,3] So if cancer has developed an ability to subvert the immune system, how is it possible to overcome this mechanism of tumor self-preservation? The burgeoning field of immunotherapy may hold some answers in creating novel treatments for cancer as well as new ways of thinking about this old disease.

The immune system is a complexity overcome by the cleverness of cancer cells. This system has been classically divided into the innate and adaptive immune systems.[2-4] The innate immune system is the first-line defense system involving anatomical barriers to infection, cytokine-mediated recruitment of immune cells, as well as complement proteins, (molecules used to identify and destroy foreign cells while recruiting immune cells). Other players in the innate immune system include macrophages that ingest and destroy foreign cells, neutrophils that secrete destructive enzymes, basophils and eosinophils that aid in eliminating parasites, as well natural killer T-cells that target foreign cells, including tumor cells. One of the ultimate results of the innate immune system is the activation of the adaptive immune system via antigen presenting cells. The adaptive immune system consists predominantly of $CD8^+$ cytotoxic T-cells that monitor and destroy infected cells, $CD4^+$ helper T-cells that identify foreign antigens to signal antibody production, and B-cells that are involved in sensing antigens and forming antibodies. This system also includes gamma/delta T-cells that share characteristics of $CD8^+$ and $CD4^+$ T-cells. Despite each of these intricate, well-regulated components, cancer cells have developed methods to overcome nearly every mechanism of the immune system.

Cancer immunotherapy is broadly defined as the ability to induce the innate and adaptive immune system to neutralize neoplastic cells. Multiple methods have developed over the past 50 years with the most interesting clinical applications unveiled only recently. These include non-cellular methods such as antibodies and drugs to regulate the immune system (Figure 1) as well as cellular based techniques to manipulate the immune system such as adoptive cell transfer (ACT) and tumor vaccines (Figure 2). These methods have shown mixed effects in different cancers again reaffirming the immense heterogeneity of cancer and difficulty in treating this disease.

A straightforward strategy to treat cancer includes inducing the immune system. Administration of the body's own signaling molecules (cytokines such as IL-2 or interferon-α) has been shown to stimulate the immune system to fight cancer (Figure 1A).[5] In fact, pegylated interferon-α2b was approved by the Federal Drug Administration (FDA) in 2011 for the treatment of melanoma.[6] These initial approaches have been expanded by recent knowledge regarding immune-modulating antibodies and cell signaling. Tumor-specific monoclonal antibody, generation is an approach that uses purified antibodies generated in the lab towards a specific tumor cell surface target.[7] Rituximab (Biogen Idec/Genentech, San Francisco, CA) is a monoclonal antibody used to target CD20 cell re-

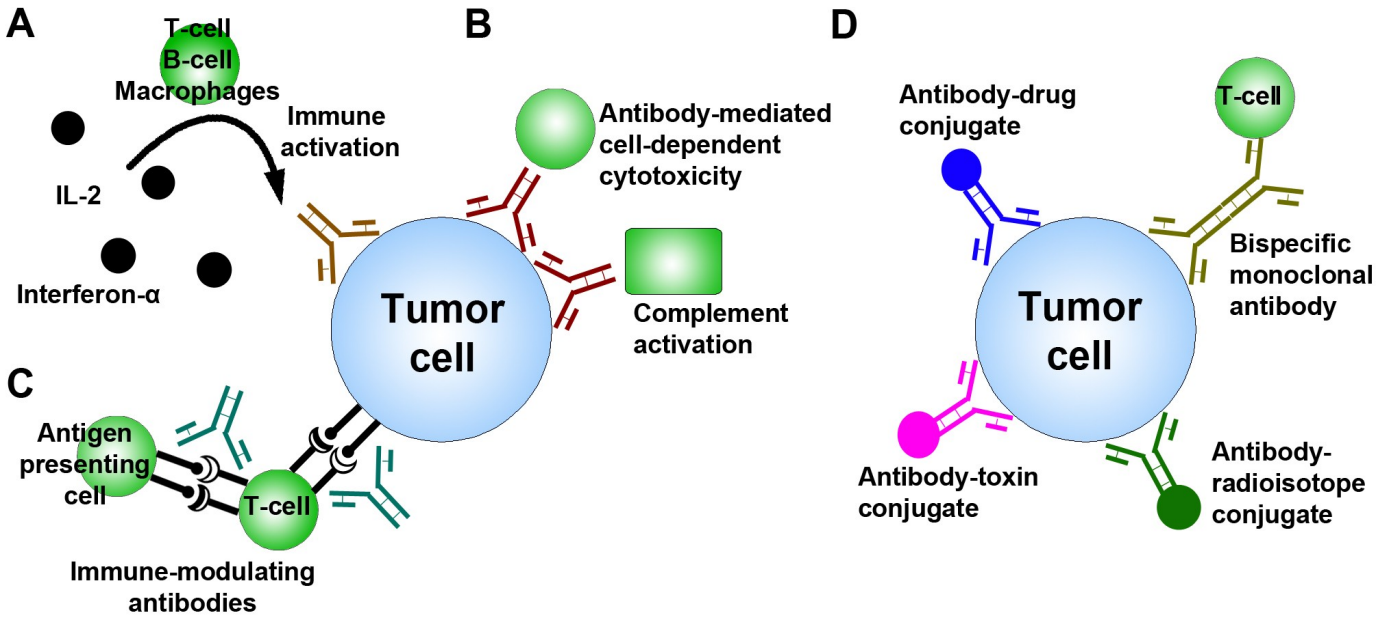

Figure 1: Non-cellular methods of immunotherapy. Various methods of immunotherapy using non-cellular means are shown. A) Treatment with interleukin-2 (IL-2) or interferon-α can stimulate the immune system to fight cancer. Examples include the use of pegylated interferon-α2b in the treatment of melanoma. B) Designed tumor-specific monoclonal antibodies can target tumor cells via induction of an immune response (Antibody-mediated cell-dependent cytotoxicity) or via activation of the immune system's complement cascade (Complement activation). Examples include Rituximab for the treatment of non-Hodgkin cell lymphoma and chronic lymphocytic leukemia as well as Trastuzumab in the treatment of breast cancer. C) Immune-modulating antibodies are used to target co-regulatory proteins that allow T-cells to interact with tumor cells or antigen presenting cells. Examples include Ipilimumab and Tremlimumab for the treatment of metastatic melanoma. D) Antibody-drug conjugates and antibody-toxin conjugates are being developed to target tumor cells. Antibody-radioisotope conjugates may allow for earlier tumor diagnosis. Bispecific monoclonal antibodies are useful for localizing the body's immune cells to tumor cells.

ceptors which has been approved by the FDA in the treatment of non-Hodgkin cell lymphoma and chronic lymphocytic leukemia, as well as several non-oncological diseases.[8] Recent studies have surprisingly shown that this antibody helps induce the immune system to kill targeted tumor cells in a process known as antibody-dependent cell-mediated cytotoxicity (ADCC) (Figure 1B).[9] The drug Trastuzumab (Genentech, San Francisco, CA), also known as Herceptin and used to target the Her2/Neu growth factor receptor in the treatment of breast cancer, has also been shown to mediate ADCC in addition to its well known effects on altering growth factor signaling of targeted cancer cells.[10]

Other novel uses of monoclonal antibodies include immune-modulating antibodies. Two new compounds, Ipilimumab (Bristol-Myers Squibb, Princeton, NJ) and Tremlimumab (Pfizer, New York, NY), have been shown to target CTLA-4 (Figure 1C)[11]. Normally CTLA-4 is a co-regulatory receptor on T-cells that binds to molecules B7-1 and B7-2 found on dendritic or tumor cells and inhibits the immune system, which can allow cancer cells to escape targeting. Ipilimumab and Tremlimumab disrupt this inhibition and have shown response rates of 10-15% with metastatic melanoma and renal cell carcinoma.[12] Ipilimumab has been FDA-approved as a first-line therapy for metastatic melanoma based on promising phase III trials.[13] Even newer therapies are looking at additional co-regulatory immune-checkpoint targets such as programmed cell death 1 (PD1) which are present in many cancers and may result in a more universal on-

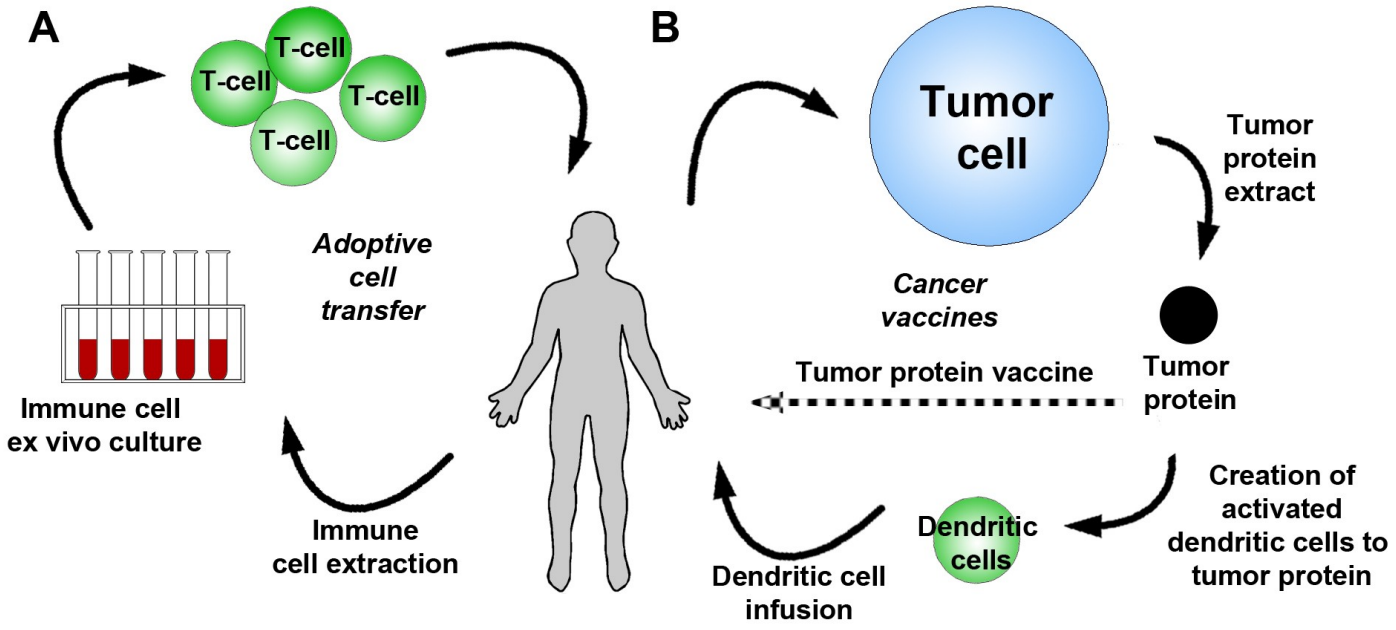

Figure 2: Cell-based methods of immunotherapy towards cancers. Various methods of immunotherapy using cellular means are shown. A) Adoptive cell transfer (ADT) is demonstrated. Tumor infiltrating lymphocytes are extracted from patients, expanded *ex vivo* in laboratory cultures, and reinfused back to patients. Engineered T-cells can also be generated in cultures before reinfusion. B) Cancer vaccines are shown. Tumor cells are extracted from patients and specific tumor proteins are extracted before either being reinjected into patients or used to sensitize patient-derived dendritic cells to target tumors. Examples include Spuleucel-T used in the treatment of hormone-resistant prostate cancer.

cological therapy.[6,14] The ability of bifunctional antibody-like molecules to bind cancer cells and retarget T-cells towards cancer cells (Figure 1D)[15] or use antibody-drug/antibody-toxin conjugates to directly target individual cancer cells (Figure 1D)[16] is also an area of open investigation. Antibody-radioisotope conjugates have also been investigated as methods to diagnose tumors earlier as well as identify disease progression sooner than current modalities. These methods suggest that non-cellular based techniques to regulate the immune system can be potent ways of treating cancer.

One form of immunotherapy that has gained momentum in recent years includes adoptive cell transfer (ACT). This technique utilizes anti-tumor T-cells that are manipulated *ex vivo* and then infused into a patient, in a similar method to bone marrow transplantation. In one study, tumor infiltrating lymphocytes obtained from patients, expanded *ex vivo* in a lab, and then re-infused in patients with metastatic melanoma showed that in addition to standard therapy, a clinical response of 34-72% was seen (Figure 2A).[17] Therapies using such multicellular treatments have shown greater efficacy than therapy with purified single cells, again highlighting the heterogeneity of cancers and their surface markers in striving to achieve personalized therapy.[18] However, the limitation of ACT involves the cumbersome cell-extraction process. Newer approaches utilize engineered T-cell receptors inserted into lab cultured $CD4^+$ and $CD8^+$ peripheral lymphocytes that can be transfused into patients.[19] ACT can achieve tumor-inhibiting activity so long as a patient's tumor possesses the required target. Combinations of ACT treatments along with standard treatments are being investigated in various early phase clinical trials for some cancers.[20]

One of the most exciting avenues in immunotherapy is the development of cancer vaccines. Initially set-

back by a variety of early clinical trial failures in the 1960s, this approach has generated renewed interest along with a recent FDA-approved treatment. Cancer vaccines involve the administration of tumor proteins to generate an immune response or immune cells (i.e. dendritic cells) sensitized to tumor proteins (Figure 2B). Spuleucel-T/Provenge (Dendreon, Seattle WA), FDA-approved in 2010 for the treatment of advanced hormone-resistant prostate cancer, involves inoculating patient-derived peripheral blood mononuclear cells with prostatic acid phosphatase linked to granulocyte macrophage colony-stimulating factor – essentially training a patient's own cells to target prostate cancer specifically.[21] In phase III trials, Spuleucel-T resulted in a 4-month overall survival benefit; The cost of this treatment, however, has been estimated to be approximately $100,000, which may limit its eventual application.[22] Vaccines towards melanoma[23], high-grade glial[24,25], breast[26], pancreatic[27], lung[28] cancers are currently in development. New knowledge of immune regulation in cancer has improved the efficacy of these approaches by using improved target antigens, high quantities of antigens to sensitize immunity, and proper co-stimulatory signals to activate immune cells.

The field of immunotherapy is emerging significantly as a viable option in the treatment of cancer. Much work has yet to be done before this dream can become a reality for many patients. In addition, new developments have dramatically altered the concept that cancers have unilaterally circumvented the immune system. Instead, various methods of inducing the immune system to fight cancer have been developed, methods which will hopefully act as precursors for the development of similar methods in the near future.

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