Immunotherapy – Concept Turned Reality

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Introduction

While using the body's own immune system as a therapeutic approach to fight cancer is not a new concept in oncology, recent successes in clinical studies are making immunotherapy a reality. Immunotherapy represents a paradigm shift. Instead of targeting cancer cells directly like radiation, chemotherapies, and some other targeted therapies, immunotherapy exploits the antitumor capabilities of resident immune cells within the body. Recent therapies have focused on using vaccines, oncolytic viruses, and antibodies aimed at blocking immune checkpoints to initiate antitumor responses [1]. The latter of these, immune checkpoint inhibitors, are being considered the "game changers" in cancer immunotherapy [2]. Although clinical experience with this type of immunotherapy is still in its infancy, the potential for immune checkpoint inhibitors to elicit durable cures has brought new hope to oncology.

Overview of the Immune System and its Role in Cancer Immunity

The immune system is a complex system responsible for recognizing and destroying foreign invaders such as bacteria and viruses as well as damaged or abnormal cells. An immune response is elicited when immune cells encounter an antigen which is a substance that is considered foreign to the body. The body uses white blood cells to provide specific and non-specific protection against foreign substances. Macrophages and natural killer cells, which provide non-specific protection, engulf foreign invaders as well as dead, diseased, or damaged cells. T cells and B cells, other specialized white blood cells, provide protection against specific targets. Effector T cells release substances toxic to cells (i.e., cytotoxic agents) that directly destroy their targets while B cells generate antibodies which tag their targets for destruction by other specialized white blood cells.

The ability of immune cells to remove diseased or abnormal cells is thought to prevent the development of cancer [3]. To effectively destroy cancer cells, an orchestrated series of events must be initiated by the immune system [1,4] as illustrated in Figure 1 [4]. As depicted in step 1, antigens, which are specific to the cancer cells from which

they originate, are released and engulfed by white blood cells such as macrophages or dendritic cells. These cells then process and present the antigen on their cell surface and are therefore referred to as antigen-presenting cells (APCs) (step 2). The antigen is presented and

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recognized by T cells resulting in the activation of effector T cell responses (step 3). These effector T cells migrate to sites where antigens are present (step 4) and move from the blood vessel into the tumor bed (step 5). Once in the tumor bed the effector T cells recognize and bind to the cancer-specific antigen (step 6) and kill the targeted cancer cell (step 7). The destruction of cancer cells releases additional cancer-specific antigens and the process continues.
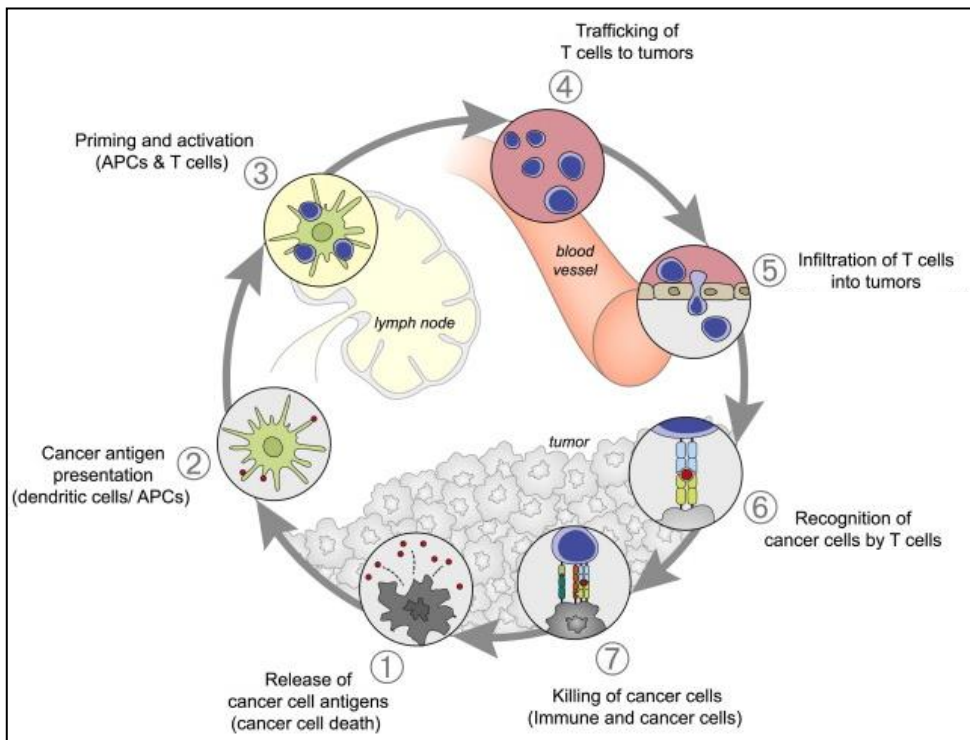

Figure 1: The immune system is a key player in the elimination and control of early tumor development as illustrated in the cancer-immunity cycle above. Figure from [4].

Tumor cells may evade immune detection through some anomaly in the cancer-immunity cycle described above. Immune suppression may occur through several different mechanisms [4,5] and may occur at any step in the cycle. For example, tumor antigens may not be produced or can go undetected (Figure 1; steps 1 and 2); antigen presenting cells may not receive the necessary signals to mature, preventing them from presenting antigens and failing to induce T cell activation (steps 2 and 3); or T cells may not receive the appropriate recruitment signals that allow them to locate the tumor microenvironment (step 4). Additionally, T cells may be unable to access the tumor if they are inhibited from attaching to and passing through the blood vessel wall (step 5). Finally, factors within the tumor environment may kill T cells, prevent them from recognizing tumor cells (steps 6), or inhibit their cytotoxic effects (step 7).

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Checkpoint Inhibitors as an Immunotherapeutic

As indicated above, one method by which tumors may suppress an antitumor immune response is by interfering and preventing T cells from destroying cancer cells. Immune cells have built in mechanisms, termed checkpoints, which are in place to inhibit immune responses [6]. Under normal circumstances these checkpoints aid in controlling immune responses to prevent over-activation and subsequent damage to healthy tissue. Exploiting immune cell checkpoints, particularly those associated with T cell responses is one mechanism through which tumor cells evade immune cell destruction.

Immune checkpoints typically work through receptor-ligand interactions. When a protein (the ligand) binds to another protein (the receptor), the downstream T cell responses are typically turned off. Blockade of immune checkpoints can be accomplished through the use of antibodies [2], which can ideally out-compete the ligand for the receptor. By blocking these receptor-ligand interactions, immune responses can be restored and tumor cells targeted for destruction (Figure 1). Recently, this concept has become a reality with the introduction of antibodies that can selectively inhibit the CTLA-4 and PD-1 checkpoints on T cells.

CTLA-4 – The first immune checkpoint receptor to be clinically targeted

CTLA-4 is a receptor protein exclusively found on T cells that, when bound with its ligand, reduces T cell activation. Under normal circumstances, CTLA-4 prevents over-activation of T cells. However, during cancer the CTLA-4 receptor becomes overactive leading to a reduction in T cell activation [2,6].

CTLA-4 was the first immune checkpoint receptor to be clinically targeted in cancer patients, specifically in those with metastatic melanoma. Targeting the CTLA-4 receptor was initially met with skepticism since CTLA-4 ligands are not exclusively found in tumors and because previous animal studies demonstrated severe immune toxicity, due to over activation of immune responses, when CTLA-4 was blocked [2]. However, in 2010, ipilimumab, an antibody against CTLA-4, became the first therapy in history to show a significant survival benefit for patients with melanoma in clinical trials. Of those treated with ipilimumab, 20% showed an increase in long term survival [7]. Although impilimumab is associated with some immune toxicities, it received FDA approval in 2011 for the treatment of melanoma.

Blocking PD-1/PD-L1

On the heels of CTLA-4 checkpoint inhibition have been therapeutic antibodies aimed at blocking the PD-1/PD-L1 checkpoint. When the ligands PD-L1, and to a lesser extent PD-L2, bind to the PD-1 receptor found on the surface of T cells, T cells become functionally inactivated. Unlike CTLA-4 which works to regulate the initial activation of T cells, the PD-1 checkpoint is present in already active T cells and regulates T cell activity at the tissue or tumor level [6]. Under physiological conditions, ligands for PD-1 are low, but several tumor types, such as melanoma, ovarian, renal, hepatocellular, and glioblastoma, express PD-L1 [1].

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Therefore, when T cells invade these types of tumor beds, PD-L1 binds to the PD-1 receptor on T cells, rendering T cells inactive and unable to destroy the tumor cells.

Several therapeutic antibodies against PD-1and PD-L1 have entered clinical testing over the past several years [2]. Most notable are nivolumab and pembrolizumab which gained FDA approval in 2014 and 2015, respectively, for the treatment of metastatic melanoma. Nivolumab is also approved for non-small cell lung carcinoma. Both drugs are antibodies that selectively bind the PD-1 receptor to prevent the PD-L1 ligand from binding. When the checkpoint is blocked, T cell activity is reinstated as are anti-tumor immune responses. In Phase III clinical studies, pembrolizumab and nivolumab were shown to extend overall survival and progression free survival [7,8] while having reasonable safety profiles. The efficacy of pembrolizumab and nivolumab, as well as additional PD-1 and PD-L1 blocking antibodies is also being evaluated in several other indications [1,2].

New Therapeutics, New Problems: Understanding Tumor Flare

An important and distinguishing characteristic of immunotherapeutics versus conventional chemotherapeutic agents is the ability of immunotherapies to induce tumor flare. Tumor flare is defined as an increase in tumor size and metabolic activity. During initial studies with antibodies against CTLA-4, it was noted that response to therapy was slower than traditional therapies. Additionally, in several instances, new lesions appeared and tumors increased in size on CT and MRI scans yet showed regression at follow-up. Specifically, 10-20% of patients treated with ipilimumab showed an increase in tumor size but eventually showed tumor control or regression with long-term survival similar to patients with initial regression [7,9]. This phenomenon is explained by the increased number of immune cells infiltrating the tumor and the additional time required by immune cells to kill the tumor cells.

Oncologists usually evaluate the efficacy of a therapeutic by monitoring and measuring changes in tumor size. Standardized criteria, for example, Response Evaluation Criteria in Solid Tumors (RECIST) [10,11], have been created and are followed to monitor tumor response and growth. Patients with progressing disease, i.e., tumor growth or newly presenting lesions, are considered treatment failures while those with shrinking and disappearing tumors are considered treatment successes. Although these criteria are sufficient for conventional treatment strategies, they are not appropriate for immunotherapies which can cause tumor flare. Therefore, new tumor response criteria, immune-related response criteria (irRC) [9], and subsequent modifications [12] have been proposed to account for tumor flare and the presence of new lesions.

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VirtualScopics provides unparalleled imaging solutions for immunotherapeutic clinical trials. In addition to having the experience and knowledge to help sponsors meet their imaging endpoints, our highly experienced and well trained radiologists provide accurate assessments of response and disease utilizing many different response criteria including irRC or irRECIST.

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