

Advances in immunotherapy for Cancer Treatment

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Abstract

Cancer is one of the leading causes of death around the world. Cancer cells display uncontrolled cell division and often times the ability to metastasize through the body. Cancer cells tend to possess genetic mutations that result in evasion of the cell cycle arrest system, inhibition of tumor suppressor genes, activation of oncogenes, and evasion of the body's immune system. Although a range of cancer treatments have been developed, they often harm healthy cells and can damage the immune system of the patient. Based on the fact that the immune system does have mechanisms for recognizing and eliminating tumor cells, many modern anti-cancer therapies, collectively referred to as immunotherapy, involve manipulating the cancer patient's own immune system to more effectively attack tumor cells. Some of these new immunotherapy-based strategies include the engineering of chimeric antigen receptor (CAR) T cells, administration of tumor specific monoclonal antibodies to induce antibody-dependent cellular cytotoxicity (ADCC), administration of monoclonal antibodies that interfere with T cell checkpoints, and administration or in vivo expression of tumor specific neoantigens to activate tumor antigen-specific T cells. These techniques have their problems, but clinical trials have demonstrated promising results in many patients, and in general are significantly less hazardous to the patients undergoing treatment than traditional chemo- and radiation-based therapies.

Keywords: Immunotherapy; Neoantigens; Immunoglobulins; Thymocyte

Abbreviations: CAR: Chimeric Antigen Receptor; ADCC: Antibody-Dependent Cellular Cytotoxicity; RB: Retinoblastoma; NKT: Natural Killer; CR: Cell Receptor; MHC: Major Histocompatibility Complex; APC: Antigen Presenting Cell.

Brief Review of Cancer

Cell division is a tightly controlled process and proceeds through a specific sequence of steps collectively referred to as the cell cycle. The standard cell cycle consists of four steps or phases; specifically, gap phase 1

(G1), synthesis (S), gap phase 2 (G2) and mitosis (M) [1]. The cell cycle is regulated by three important checkpoints that ensure that critical processes are occurring normally. During G1, the cell begins to synthesize genetic and biosynthetic materials required for growth and the support of two daughter cells, and these properties are assessed at the G1 checkpoint. The G1 checkpoint also assesses the genetic integrity of the cell and the cycle will be inhibited if DNA damage is detected [1]. Once this is complete, the cell passes through the checkpoint into the S phase during which DNA replication occurs and the cell's chromosomes are duplicated. The next phase is the G2 phase, which is where additional cell growth occurs as

the cell prepares for mitosis. However, before the cell is allowed to enter the M phase, it must go through a second checkpoint. This checkpoint also assesses if adequate cell resources are present and if DNA duplication has been successful [2]. Once the cell has cleared this checkpoint it will progress into the M phase which results in cell division. A checkpoint within the M phase assesses spindle attachment which is required for proper chromosome segregation into the two daughter cells. Following mitosis, the cells again enter G1, grow to normal size, and typically enter a resting phase (within G1) called G0. Cells in G0 have essentially exited the cell cycle and will not divide again until receiving the proper stimulation to do so [1].

G0 is maintained by cellular proteins called tumor suppressor proteins [3]. The most notable tumor suppressor proteins are retinoblastoma (Rb) and p53. Briefly, Rb prevents the G1/S phase transition by binding and sequestering critical transcription factors that are required to activate the cellular genes required for entry into S phase. Under conditions when cell division is required, Rb can be phosphorylated by cell cycle-related kinase enzymes and in the phosphorylated state Rb releases the S phase transcription factors and the cell cycle is induced to move forward [4]. Levels of p53 are typically very low in normal cells as p53 is targeted for degradation soon after being produced. However, under conditions of cell stress, such as checkpoint failures and other forms of cellular stress, p53 is stabilized through post-translational modifications such as phosphorylation and acetylation, and in this form activates transcription of cellular genes that induce cell cycle arrest or programmed cell death (apoptosis) [5]. In these ways Rb and p53 maintain control of the cell cycle and can induce cell death if warranted. Not surprisingly, mutations that result in the loss of function in Rb and/or p53 can result in loss of G0 control and uncontrolled cellular division.

The hallmark property of cancerous cells is their uncontrolled division. Cancer cells typically contain numerous genetic mutations, many of which result in dysregulation of the cell cycle [6]. Cancer cells typically contain mutations in two general classes of genes; specifically, they tend to contain mutations within genes called proto-oncogenes and they contain mutations in tumor suppressor genes, which as discussed earlier play an important role in preventing cell cycle progression. Proto-oncogenes tend to encode proteins that promote cellular division and under normal conditions the expression of these genes is tightly regulated to ensure that cells are stimulated to divide only in proper conditions [7]. Cancer cells tend to contain one or more

mutated proto-oncogenes, and if these mutations result in the generation of a cancerous cell, the gene is typically referred to as an oncogene to indicate the association between the gene and the transformed phenotype of the cell [8]. Conversion of a proto-oncogene to an oncogene can result from simple point mutations, insertions, deletions, gene duplications, transpositions or gene fusions. These genetic changes can result either in overexpression of the normal proto-oncogene which by itself can induce cell growth/division, or in the expression of altered gene products such as proteins that can promote cell transformation [7]. In addition to possessing mutations in proto-oncogenes, cancer cells also tend to contain mutations that inhibit the function of one or more critical tumor suppressor gene, such as p53. Collectively, the multitude of mutations present in cancer cells serves to promote cell division and to inhibit the normal cell cycle controls, including cell cycle checkpoints, that under normal conditions can bring cell division to a halt.

The Immune System's Recognition of Cancer

The adaptive and innate immune systems have evolved to differentiate between self-antigens, which a properly functioning immune system will ignore or tolerate, and dangerous non-self antigens, that under normal circumstances will elicit an immunological response [9]. As will be explained below, the immune system does have ways of responding against certain types of self-cells, such as tumor cells. The two cell types that play the most important role in identifying and killing tumor cells that arise in the body are T cells (effector T helper cells and cytotoxic T lymphocytes [CTLs]) and natural killer (NK) cells.

As components of the adaptive immune system, individual T lymphocytes express unique forms of an antigen receptor called the T cell receptor (TCR). Antibodies serve as the corresponding antigen receptor for B lymphocytes. The TCR consists of two interacting glycoproteins (α -chain and β -chain) expressed on the surface of the T cell [10]. During T cell development in the thymus, the genes that encode the α -chain and β -chain proteins are rearranged in a process called VDJ recombination which is a randomized process that generates an almost limitless number of different TCR protein sequences [10]. These differences are not present throughout the length of the TCR proteins but instead are localized to the N-terminal regions of the proteins called the variable domains. The TCR interacts with very specific self-proteins called major histocompatibility complex (MHC) glycoproteins and the peptide fragments that they bind to (peptide/antigen presentation) [10]. There are

two general types of MHC; the first referred to as MHC class I which are expressed by all nucleated cells of the body, and MHC class II, which is expressed only on dendritic cells, B lymphocytes, macrophages, and thymic epithelial cells [10]. The primary function of the MHC complex is to bind peptide fragments that have been generated from proteins synthesized within the cell (MHC-I) or peptide fragments generated from exogenous proteins that were taken up by the cell from the extracellular environment (MHC-II) and to present these peptides to T cells [9]. During their development in the thymus, developing T cells generate their unique TCR and essentially test its MHC/peptide binding properties against a wide range of self MHC/peptide complexes presented on the surface of thymic epithelial cells and thymic dendritic cells. Because the MHC/peptide binding characteristics of the TCR arise as a result of random genetic recombination events and are not programmed, many of the TCRs will actually bind with high affinity to self MHC/peptide complexes, which is dangerous because high affinity TCR binding leads to T cell activation and differentiation into an effector cell capable of mounting an attack against the cells possessing the offending MHC/peptide. To control for autoimmunity, this type of T cell is either eliminated in the thymus through the process of apoptosis, or the cell is reprogrammed into an immunosuppressive cell called a regulatory T cell (Treg) [9]. Thus, T cells that leave the thymus and spend the rest of their existence circulating through the body surveying for their specific antigen should be self-tolerant and should only be capable of responding to antigens that were not expressed in the thymus during their development [9].

Ideally, naïve T cells will only bind with high affinity to a self-MHC complex presenting a peptide derived from a non-self source such as a peptide product of a viral or bacterial protein. In this context a robust T cell response is desirable. Since tumors consist of cells derived from one's own body (self), it is logical to assume that the immune system will tolerate them and not mount an attack against them, as an immune response against self-tissues is defined as autoimmunity, which is almost always harmful. However, there are several key differences between normal cells and cancerous cells that enable components of the immune system to selectively mount an attack on tumor cells, typically without causing harm to healthy, non-cancerous tissues. These alterations can either be the expression of a mutation, thus altered self-proteins called neoantigens (as explained below) or the diminished expression on MHC-I glycoproteins on the cell surface [11].

Due to the genetic instability of tumor cells these cells exhibit a high mutation rate which can result in the expression of self-proteins with altered amino acid sequences. The altered self-proteins are termed neoantigens, and can be treated by the immune system as foreign proteins [11]. Because these neoantigens were not expressed in the thymus during T cell development, T cells with TCRs that are able to bind with high affinity to peptides derived from them were never negatively selected against these peptides, and many T cells circulating in the body possess TCRs that will bind with high affinity to these peptides when they are complexed with MHC on the tumor cell surface [10]. In the case of CD8+ Tc cells, this interaction can lead to the generation of CTLs capable of killing the tumor cell. Naïve Th cells can also be activated by these antigens and mediate a cellular anti-tumor response. The fact that T cells, and even B cells that possess antibodies, can be activated to respond against cells expressing neoantigens is relevant to the neoantigen vaccine anti-tumor strategies described below.

NK cells also play an anti-tumor role in the body, but NK cells are not antigen-specific like B and T lymphocytes, and instead tend to respond against cells that lack normal expression levels of MHC-I on their surface [12]. Many tumor cells decrease expression of MHC-I, presumably as an evolution-based strategy to evade detection by Tc cells. NK cells also participate in an immune process called antibody-dependent cellular cytotoxicity (ADCC). Briefly, ADCC occurs when an antibody binds to an antigen expressed on a cell surface through its Fab region, and the Fc region of the bound antibody is then engaged by an activating Fc-receptor of a cytotoxic cell such as an NK cell [12]. Signaling through the Fc-receptor can trigger the cytotoxic cell (e.g. NK cell, macrophage, eosinophil) to release cytotoxic substances and/or induce the antibody-targeted cell to initiate an extrinsic programmed cell death pathway (apoptosis). This activity of NK cells is relevant to the use of tumor-targeted monoclonal antibodies as will be discussed later in the report.

CAR T Cell Therapy

A cell destined to become a T cell begins its life in the thymus which is where it begins its developmental process as a cell called a thymocyte that possesses no antigen receptor and has no antigenic specificity. This cell ends the developmental process as a functioning naïve T cell that possesses an antigen-specific surface receptor called the T cell receptor (TCR) and has committed to functioning either as a T helper cell (CD4+) or T cytotoxic cell (CD8+) [10]. All mature T cells express a TCR that

binds specifically to a single MHC allo type presenting a single peptide fragment. T helper cells interact with peptide presented in the context of MHC-II molecules and T cytotoxic cells interact with peptide presented by MHC-I molecules [9]. Due to the random process by which TCR genes are recombined during T cell development, each T cell is essentially unique with respect to its antigen binding specificity. For a naïve T cell to become activated and differentiated into an effector T cell with the ability to participate in an immune response, the T cell must bind to its specific MHC/peptide complex, and be stimulated through two fundamental signaling pathways [10]. Typically, activation of a naïve T cell is only achieved if the T cell is presented antigen by a professional antigen-presenting cell (APC). The most potent APC is the dendritic cell, but B lymphocytes and macrophages can also function as APCs capable of activating naïve T cells. High affinity binding by the TCR is sensed by the CD3 component of the TCR complex, and in response, CD3 initiates signal transduction pathways that culminate in transcription of T cell activation-related genes [9]. However, signaling through CD3 by itself is not sufficient to activate the naïve T cell. The second critical cell to cell interaction that is required for activation of a naïve T cells involves a surface receptor on the T cell called CD28 (i.e. the T cell co-receptor) and a protein called B7 (CD86) that is expressed on the APC [9]. Like CD3, upon binding its ligand CD28 initiates a signal transduction pathway that leads to altered gene expression and eventual T cell differentiation into an effector T cell. Although both of these critical receptor/ligand interactions occur outside of the cell, it is the cytoplasmic domains of CD3 and CD28 that are responsible for interacting with cytoplasmic components of the signal transduction pathways [10].

T cells, particularly Tc cells, play an important role in identifying tumor cells and activated Tc cells (referred to as CTLs) are capable of killing these dangerous self-cells. As discussed earlier, many tumor cells express mutated forms of self-proteins (neoantigens), and the adaptive immune system essentially treats these proteins as foreign proteins that should be responded against [11]. However, due to the fact that each T cell is specific for a single peptide sequence, only rare T cells display a specificity for the neoantigens of any given tumor. A novel technique to expand the number of T cells that display a receptor capable of interacting with tumor-specific neoantigens has been developed and tested. This technique involves the engineering of T cells to express what is termed a Chimeric Antigen Receptor (CAR). T cells that express CARs are referred to as CAR T cells and these are usually created by modifying the patient's own T cells, though in the future it may be possible to use "off the

shelf" CAR T cells that are not derived from the patient being treated. The fundamental components of the CAR are an extracellular domain that contains a single chain antibody that binds specifically to the neoantigen of interest [13]. This domain is linked through a transmembrane region to two cytoplasmic protein domains that represent the signaling domains of CD3 and CD28, respectively [13]. The recombinant CAR DNA is constructed in the laboratory through routine recombinant DNA techniques, and then transduced into T cells derived from the patient. Often times the CAR DNA construct is introduced into the T cell using retrovirus-based vectors, or more recently through the use of CRISPR-CAS9 systems [14,15]. Expression of the CAR does not eliminate the T cell's normal antigen specificity as defined by its natural TCR, but it does bestow a new specificity for the surface expressed neoantigen of the tumor [11]. This means that any T cell can be isolated from the patient, and regardless of its natural MHC/peptide specificity, the cell can be converted into a cell that will be activated upon binding to the tumor expressed neoantigen. The basic sequence of events involved in this process are:

- 1) identification of tumor specific neoantigens,
- 2) generation of a monoclonal antibody that binds to a neoantigen epitope,
- 3) construction of the CAR DNA construct,
- 4) harvesting of T cells from the patient and transformation of these cells with the CAR DNA,
- 5) expansion of these cells in culture, and
- 6) reintroduction of the modified CAR T cells into the patient [16].

When the single chain antibody component of the CAR binds to the neoantigen on a tumor cell, the cytoplasmic components of the receptor initiate signal transduction events through the normal CD3 and CD28 pathways, thus triggering the naïve T cell to differentiate into an effector cell (e.g. CTL) capable of mounting an attack on the tumor cell.

A different approach to CAR T cell therapy can be used for some types of tumors that express a known self-antigen that is not a neoantigen. In this strategy, the antigen-binding component of the CAR is specific for a surface antigen that is expressed universally on a terminally differentiated cell type. For example, a surface protein called CD19 is expressed on all B cells, and CAR T cells expressing a CAR that binds to all CD19-positive cells [17]. In cases where the tumor is of B cell origin (e.g. B cell lymphoma, multiple myeloma) CD19-targeted CAR T cells will attack both cancerous B cells as well as non-transformed B cells. B cell depletion using this approach

does not have long term effects as the bone marrow constantly replenishes the B cell population of the body [9,17]. Clinical trials of this therapeutic approach have resulted in long-term cancer remission in many study participants. Utilizing the CD19 method, blood malignancies have shown to be susceptible to CAR T cell treatment with a complete remission occurring in between 70% to 94% of treated patients [17]. In some individuals this strategy may only have short-term benefit as variant B cells from the tumor can evade the CAR T cells by simply mutating the CD19 protein or eliminating expression of this protein. This phenomenon has been identified in patients that originally responded well to the treatment but later on experienced the return of the cancer [17]. CAR T cell therapies are very expensive and labor intensive, which may limit its full potential in the clinic. In principle the cost of this therapy could be markedly reduced if a standard off the shelf CAR T cell product could be produced, but at the current time this treatment still requires the harvesting, modification, and expansion of a patient's own T cells [13].

Targeting Immune System Components to Tumor-Specific Antigens

As explained above, the immune system has evolved to tolerate self antigens and to respond specifically to dangerous non-self antigens such as proteins expressed by pathogenic microbes. Although tumor cells are derived from self cells, they do express antigens that are unique to the tumor and which were not expressed elsewhere in the body (e.g. bone marrow or thymus) during B cell and T cell development [10]. Therefore, some of the B and T lymphocytes circulating through the body do possess antigen receptors (immunoglobulin and TCR, respectively) that are capable of binding the tumor-specific antigens [9]. These tumor-specific antigens are typically referred to as neoantigens and represent mutated versions of normal cellular proteins [11]. Neoantigens expressed on the cell surface are accessible by the immunoglobulins expressed by B cells and by free antibody [11]. Peptide fragments derived from neoantigens can be recognized by T lymphocytes through their TCR when the peptides are presented on the tumor cell surface in complex with MHC. Based on the fact that tumor cells can be differentiated from healthy cells by their expression of neoantigens, the opportunity exists to generate the appropriate neoantigen in the laboratory, and administer them to a patient in the form of a vaccine in order to induce an immune response that will target cells expressing the vaccine antigen [18]. The first step in this process is to identify neoantigens that are specific to a patient's tumor [18]. This is typically done by comparing

the genomic sequences of tumor and non-tumor cells. Once mutated genes are identified the predicted sequence of the neoantigens can be predicted, enabling the correct protein to be produced under laboratory conditions [11,18]. In one clinical trial using this approach a computer algorithm was used to predict and twenty neoantigen sequences from a tumor, and these peptide sequences were then synthesized and administered to the patient by subcutaneous injection. This resulted in induction of moderate to strong T cell responses [18]. In another trial, an RNA that encoded for neoantigens was encapsulated within lipid nanoparticles and then injected into a different set of patients. Most of these patients became cancer free, though a minority of the patients eventually relapsed. These nanoparticles were shown to be taken up by dendritic cells. An altered version of this approach involves the isolation of dendritic cells from a cancer patient, mixing with the RNA-containing nanoparticles with these cells, expanding and artificially activating the DCs, and then reintroducing the cells to the patient in the hope that the introduced RNA will express the neoantigens in the DCs which in turn will process the neoantigens and present peptide fragments to T cells [18]. Presumably, T cells stimulated in this way will be primed to mount an attack on tumor cells expressing the same peptide sequences on their surface. The use of recombinant virus-based vectors to express neoantigens *in vivo* has also been studied [19].

In addition to using neoantigens as vaccines to induce an immunological attack on the tumor, it is also possible to take advantage of the fact that some cells that cause specific types of cancer (e.g. breast cancer, multiple myeloma, melanoma, B cell lymphoma) tend to express similar antigens regardless of which individual the tumor arises in. For example, tumors that arise from B cells (e.g. B cell lymphoma or multiple myeloma) will express normal B cell surface antigens such as CD19 and CD20. These cells can be targeted for destruction through the administration of monoclonal antibodies that bind to these antigens. In this case, binding between antibody and the tumor cell can lead to destruction of the cell through the mechanism of antibody-dependent cellular cytotoxicity [3]. Unlike neoantigens, these normal cell proteins are not restricted to the B cell tumors and normal, non-transformed B cells will also be targeted by this treatment. However, since B cells are readily replaced by a normally functioning bone marrow, destruction of all B cells (tumor cells and healthy cells) in a cancer patient should not have long term negative consequences [3,9].

One such drug that has been created using this rationale is called Rituximab. Rituximab is a monoclonal

antibody that binds to a protein called CD20 which is present on all mature B cells [20]. B cells that bind Rituximab on their surface are susceptible to killing by NK cells or by the activation of the classic complement cascade [20]. Alemtuzumab is another monoclonal antibody that binds to a cellular protein called CD52. CD52 is expressed on lymphocytes and monocytes. Tumors arising from these cell types can be targeted with this drug which works through a mechanism similar to that of Rituximab [21]. Although these drugs induce the destruction of many healthy cells that also express CD20 and/or CD52. Clinical trials have demonstrated that the body is able to replenish the cells and within six months leukocyte levels are within a normal range [21]. T cells are particularly affected by this treatment however and in some patients, it took over a decade to completely replenish their CD4+ and CD8+ cells [21]. One other drug that uses a similar mechanism of action is Brentuximab-vedotin. This drug is a monoclonal antibody that binds to CD30, which is present on activated T cells, B cells, and NK cells but has also been seen in different malignancies (e.g. Hodgkin's lymphoma, anaplastic large cell lymphoma, and germ-line malignancies etc.) [22]. However, this drug differs from the other two in that it induces apoptosis of the target cell. This is accomplished by a drug called monomethylauristatin A (MMAE) which is conjugated to the monoclonal antibody and thus is target to the specific cells that the antibody binds to [22]. The antibody and MMAE are taken up by the target cell via receptor-mediated endocytosis and once inside the cell, the MMAE molecules bind to tubulin inside the cell. This binding process disrupts the microtubule network within the cell and induce unscheduled entry into the G2/M phase of the cell cycle leads to apoptosis of the cell [22]. In addition to this, a small portion of this MMAE seeps out of these cells and gives it the ability to kill surrounding cells in the tumor microenvironment.

Checkpoint Inhibiting Antibodies

Just as it is important for a naïve T cell to be able to be activated from a resting state and transition into an effector cell capable of participating in an immune response against a harmful invader, it is also important for activated T cells to be able to transition out of an effector state when the target of the immune response (e.g. microbial infection) has been brought under control or eliminated [9]. Suppression of T cell responses can be achieved through a range of processes, including production of immunosuppressive cytokines, actions of regulatory T cells (Tregs), and through the expression of specific proteins called negative regulators or check point proteins on the surface of effector T cells. Two well-

characterized negative regulator proteins are called cytotoxic T lymphocyte-associate protein 4 (CTLA-4) and programmed cell death 1 (PD-1) [3,9]. When either or both of these surface-expressed proteins engage their specific ligand on other cells the activated T cell receives inhibitory signals and becomes less likely to proliferate or to remain in the activated state.

Many non-tumor cells such as macrophages and dendritic cells infiltrate tumors and can play a positive role in supporting anti-tumor T cell responses through their role as an APC [9]. These cells can deliver both of the stimulatory signals required to activate T cells (through expression of ligands for the TCR and CD28). As discussed earlier, it is the B7 protein on the APC that is engaged by CD28 and this receptor/ligand interaction delivers the co-stimulatory signal required for T cell activation [10]. Interestingly, CTLA-4 also binds to B7 but this interaction does not lead to T cell stimulation. Instead, this interaction leads to removal of B7 from the APC surface, thus decreasing the likelihood that signaling through CD28 will occur. Therefore, CTLA-4 functions by preventing T cell activation, and when this occurs within the tumor microenvironment, it results in decreased T cell responses against the tumor [3]. CTLA-4 expression levels increase on activated effector T cells and also on T cells that enter a state called T cell exhaustion. T cell exhaustion typically occurs in activated T cells that have participated in an immune response to a chronic infection that has resisted elimination over a long period of time, or that have engaged in a prolonged anti-tumor response that has not resulted in the elimination of the tumor [9]. Exhausted T cells tend to upregulate expression of CTLA-4 and PD-1, thus these cells become prime targets for deactivation and become less effective participants in the immune response.

Tumor cells often up-regulate their own expression of a PD-1 ligand called programmed cell death 1 ligand (PD-L1). Binding of PD-1 to PD-L1 also results in deactivation of the effector T cells, and therefore, expression of PD-L1 by cells of the tumor actively inhibits the anti-tumor response [23]. As noted above, expression levels of PD-1 increases on exhausted T cells, and T cell exhaustion is also common in tumor responses.

Due to the fact the B7/CD28 and the PD-1/PD-L1 interactions are detrimental to anti-tumor T cell responses, it became clear that interfering with/preventing these interactions could, in theory, provide clinical benefit by enhancing anti-tumor responses by T cells [23]. In fact, several monoclonal antibody-based drugs (e.g. Ipilimumab, Pembrolizumab,

and Atezolizumab), which individually bind either to one of these receptors or ligands have proven to be effective in enhancing the anti-tumor activities of T cells, and in improving clinical outcomes. Ipilimumab is an anti-CTLA-4 antibody that binds to CTLA-4 expressed on the surface of the T cell. This interaction prevents CTLA-4 from binding to B7 and serves to maintain T cells in the activated state [3]. Pembrolizumab is an antibody designed to block PD-1 receptors expressed on the T cells. This interaction prevents binding between PD-1 and the PD-1L expressed by the tumor cells. Similarly, a drug called Atezolizumab is an antibody that binds to the PD-L1 ligand expressed on tumors themselves, thus preventing the downregulation of effector T cells through the PD-1/PD-L1 interactions. Clinical trials have shown that the best antitumor activities are in patients who have Hodgkin's lymphoma, as this cancer seems to over express the PD-L1 ligand and makes it an easy target of anti-PD-L1 antibodies [23]. Some undesirable side effects of using these antibodies include enhanced inflammatory responses in some patients, which could be managed through the use of steroids [9].

Concluding Remarks

Only heart disease kills more Americans on a yearly basis than cancer. Historically, cancer treatments have been based on the use of drugs (chemotherapy) or radiation-related therapies that target dividing cells. Although chemo- and radiation-based therapies can eliminate cancers in some cases, they tend to affect many non-cancerous cells and are often very poorly tolerated by the cancer patient [24]. It has long been understood that the body's own immune system does have the ability to differentiate between cancerous and non-cancerous cells, and that several effector cells in the body have the ability to specifically kill transformed cells of the body. Unfortunately, cancer cells involve immune evasion strategies that limit the effectiveness of the immune system and result in continued tumor growth. The field of immunotherapy employs strategies to augment the immune system's anti-tumor activities, and the four immunotherapy strategies described in this report have shown significant promise and has generated a great deal of hope in the field of cancer research. The 2018 Nobel prize in Physiology/Medicine was recently awarded to an American researcher and a Japanese researcher who have pioneered the field of immunotherapy [25,26]. Although the field of immunotherapy is relatively new, significant progress has been made, and additional progress is anticipated. One can only hope that the current immunotherapy techniques that are currently in use or under development; specifically, the use of tumor-target

monoclonal antibodies to induce ADCC, the use of monoclonal antibodies to inhibit T cell checkpoint blockades, the use of CAR T cells to seek out and destroy cancerous cells, and the identification and administration of neoantigen vaccines, will lead to additional immune-based strategies for enhancing the cancer fighting capabilities of the patient's own immune system to bring about a cure for cancer [27,28].

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