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Cancer Immunotherapy by Harnessing Innate Immunity - A Brief History, Mechanism, and Future Applications of the Therapy

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Abstract

Cancer- 'The Emperor of all Maladies'- a moniker coined by the acclaimed author Siddhartha Mukherjee, continues to be the one of the devastating diseases. Despite spending billions of dollars of research funds, researchers are still at a bay in the war on the cancer diseases. However, recent therapeutic development of harnessing one's own immune system power to fight cancer is showing a slim advantage in favor of the researchers. In this process, the body's immune system is 'trained' to not only recognize and attack specific cancer cells, but also boost immune cells to help them eliminate cancer. Success stories of the immunotherapy have started to trickle down and a greater understanding of the mechanism, challenges, and application will allow new and existing researchers to develop the technology further. With this aim in focus, this review paper discusses the history, the mechanism, applications and future potential of this scintillating technology to fight cancer. A review of the potential applications and the regulatory environment for this technology will help reader develop a better understanding of this novel and unique approach to fight cancer which past decades have only produced treatments that could not lengthen survival rates significantly.

Keywords

Immunity, Immunotherapy, Cancer, Antibody, T-cells, Tregs

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1. Introduction and Background

In general, immunotherapy is the practice of using the immune system (innate or adaptive) of the human body to better the health of the patient. This broad principle can be and has been applied to a variety of problems: allergies, diseases of self-incompatibility, and the use of inoculations to prime the immune system and prevent infections in the first place [1]. The scope of this paper is limited and will focus solely on the application of immunotherapy to human cancers.

In the broadest possible sense, the theoretical basis of immunotherapy is that the body already possesses a means of fighting infections. These means are far beyond our current capacity to promote human health and require significantly less human intervention in bringing about a cure. The idea of using the body's own defenses to cure diseases, like cancer, has long been a dream in the medical community but, as we will see, one that has yet to be fully realized [2, 3]. Rather, focus in treating disease generally, and cancer specifically, has been on chemotherapeutic methods rather than on immunotherapeutic ones.

1.1. History

The concept of harnessing the immune system to fight against

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diseases started centuries ago. People in Turkey practiced a procedure named variolation, in which heathy people are immunized to smallpox by inhaling dried smallpox scabs collected from infected individuals. In 1718, when the wife of the English ambassador in Istanbul noticed the immunizational effect of variolation on the Turkish population, she had the procedure performed on her own children. Years after that, in 1798, the English physician Edward Jenner inoculated an 8 years old child with pus from cows infected with cowpox. After that, he inoculated the child with smallpox. The first exposure to the cowpox immunized the child for smallpox and the child did not develop smallpox. Those initial experiments were followed by the development of several bacterial vaccines in the 20th century.

The most widely cited example of an immunotherapeutic approach to cancer is the much-celebrated case of Dr. William Coley [4]. In the 1890s, Dr. Coley noticed that one of his patients was found in complete remission of his cancer following an otherwise ordinary infection by *Streptococcus pyogenes*. At the time, the germ theory of disease was only recently being widely accepted and the evidence indicates that Coley had little formal understanding of what processes might be at work in the cure he observed. Nevertheless, Coley continued to use this therapy with his patients. He developed a more specific mixture of infections (both living and dead viruses) to apply to his patients, which eventually became known as Coley's Toxin [5]. He did manage to cure some of his patients using this method, but the cost in suffering to the patients was great, and the cure itself was not understood [5]. Research since then suggests that the immune response stimulated by the pathogens somehow resulted in cancer fighting properties.

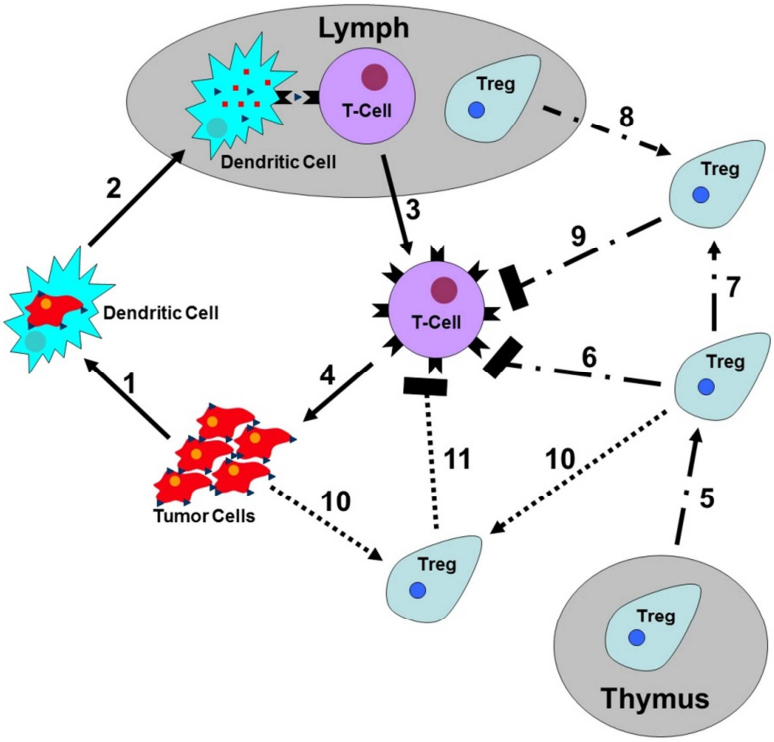

Figure 1. Figure modified and simplified from [9, 10].

This figure illustrates three separate processes involved in the bodily immune response to cancer. The arrows types indicate the order of process discovery: solid arrows indicate the cancer immune response as it was first understood in the context of the classical antibody-antigen specific immune response. The dot-dash arrows indicate the later discovered natural bodily regulation and inhibition of the specific immune response. The dotted arrows indicate the most recent knowledge that tumors somehow appropriate this natural regulation machinery for their own protection.

Cancer Immune Response under the Classical Model: Four basic steps 1. Dendritic cells ingest whole or partial tumor cells. 2. Either in a lymph node or lymph vessel the dendritic cell, now presenting an antigen for the tumor, encounters an inactivate/unspecialized T-cell. 3. The T-cell is activated by binding the antigen presented on the surface of the dendritic cell. 4. The T-cell differentiates by producing more receptors to recognize and destroy cancer cells.

Lymphocyte Regulation: Two main pathways. 5. T regulatory cells (Tregs) are produced naturally in the thymus and recognize T-cells whose antibody configuration matches the body's own cells. 6. These natural Tregs are used by the body to prevent accidental autoimmune responses by suppressing

these T-cells. 7. These Tregs can undergo further differentiation in order to suppress specific incidences of harmful autoimmune response. 8. Highly specialized Tregs can also be produced directly either in the lymph or at the site of the immune response itself. 9. These also function to downregulate T-cell activity.

Cancer Appropriates Lymphocyte Regulation Machinery: Exact Pathways unknown. 10. Cancers recruit Tregs and use them to downregulate the T-cells targeted against them. Since the Tregs arise in the cancer microenvironment it is thought that they are recruited, presumably by some signal, directly by the tumor, without using the lymph system as an intermediary. 11. Once recruited, however, the Tregs appear to function in exactly the same way as naturally produced Tregs. The function is so similar that the same processes that downregulate natural Tregs also downregulate cancer-induced Tregs.

It was only with later work that immunotherapy came to have a formal theoretical basis. This theoretical basis was a direct result of both the wide acceptance of the germ theory of disease as well as the subsequent virological studies that allowed for an understanding of the human immune system [6]. It was recognized that the human adaptive immune system made a very large number of random antibodies, molecules which are used to recognize novel, harmful, foreign substances (antigens) in the body. Through a self-feedback loop, the body amplifies antibodies that 'discover' an antigen, allowing the antigens to be effectively flagged and destroyed [6].

1.2. Recent Developments

The above outline for the human immune response suggested immediate applications for human health, and several important vaccines were developed as a result [7]. Yet, cancer was largely ignored in all of this. Cancer was not a major public health concern until life expectancy increased dramatically in the early and middle 20th century. Historically, most people died of other afflictions before cancer. Moreover, cancer treatments initially focused on the use of chemicals and this approach predominated even once cancer became a public health issue (Hewitt 1979). Immunotherapy was only recognized as a possible treatment for cancer after theoretical advances illuminated Dr. Coley's work. Moreover, there has been a number of historical shifts in the optimism of the medical community for the use of immunotherapy as an affective cancer treatment [2, 5]. The opinion of the medical community surrounding the applicability of immunotherapy to cancer largely paralleled the developments in immune system theory [2, 5].

For example, it was recognized that cancer cells did seem to present certain unique antigens (neoantigens). This suggested that, at least theoretically, cancer cells could be targeted by the immune system [8]. Under this theoretical climate, cancer seemed on the verge of defeat before the conquering forces of immunotherapy. All that was needed was the identification of antibodies specific to unique carcinogenic antigens and the immune system of the body would seek out and destroy all cancer cells. Thus, initial trials in cancer immunotherapy worked under the assumption that the major problem (the reason the body did not mount a spontaneous immune response against the cancer) was that there were not enough of the proper antibodies present to successfully recognize the cancer and prompt a T cell response to eradicate it (Figure. 1).

Gross stimulation through antibody injection or B cell stimulation had limited success in treatments, however (for the exception see reference 11). Furthermore, it was noted that, in many cases, even when heavily stimulated, the immune system by and large did not attack the cancer cells. Three key bits of information then came to light. First, it was recognized that any given tumor (or cancerous infection) is heterogeneous [12]. Thus, not all of the cells of a given tumor present the same antigens. This makes it difficult to fully eradicate a cancer by simply inducing an immune response for a single or even group of antigens. Second, and somewhat more importantly, it was found that tumors *blocked* immune response in two ways, one active and one passive [13]. Passively, the protein coats of the tumor cells were still recognized by the T cells as "self" and thus the innate bodily system designed to destroy self-recognizing antibodies kept the cancer cells insulated from any immune response. Actively, the cancer cells also induced the response of T regulatory cells (see more about this below) that are naturally used by the body to downregulate the function and production of immune lymphocytes and other processes responsible for stimulating the immune response, preventing autoimmunity (Figure 1). Third, it was recognized that the tumor microenvironment was something that needed to be considered in treatment. The cancer cells largely insulate themselves from the rest of the body and heavily modify their living space [14]. This means that applying general treatments to the whole body is largely ineffective - be they chemical or immunotherapeutic. Rather, targeted approaches were needed. These discoveries led to an era of pessimism with regard to the clinical possibilities for cancer immunotherapy.

Most recently, taking these discoveries into account, there has been a shift in attention from inducing or over stimulating the immune response of the patient (which really isn't the problem) to working to destroy the ability of the cancer cells to inhibit the immune response. The biggest area of research is in removing the ability of the tumor (or cancer) to produce the suppressor molecules that inhibit the bodily

immune response against it [13].

In spite of all this, there is presently another sense of optimism surrounding immunotherapy. Effective means of disabling cancer immunosuppression have resulted in a fresh batch of success stories [15]. The future is far from clear, however. Immunotherapeutic approaches to cancer seem to be effective in only a subset of patients. Thus, as will be seen below, the trend is to combine immunotherapy with chemotherapy and other approaches to cancer treatment.

2. Cellular Mechanism

The human body possesses both an innate (non-specific) and an adaptive (specific) immune system. Cancer appears to be able to evade both (which is why it ultimately kills the patient). The basic idea of immunotherapy is to correct this, allowed the body to recognize the cancer as an undesirable foreign element, and destroy it. Cancer immunotherapy has attempted to make the correction both in the innate and adaptive immune systems but has focused mostly on the latter. The most well-known example of an attempt to use the innate immune system against cancer is the very first immunotherapy treatment for cancer: Coley's Toxin [4]. Coley's Toxin is not specific to cancer in any way. It is simply a mixture of two viruses [5]. The toxin works because the injection of the virus prompts the response of a type of lymphocyte known as a natural killer (NK) cell. These cells are part of both the adaptive and innate immune systems. In the adaptive immune system, they can destroy cells tagged with specific antigens. As a part of the innate immune system, however, they are capable of recognizing and destroying cells infected by foreign entities. The NK cells also are responsible for destroying cancerous cells that arise in the body naturally from time to time [6]. Thus, the addition of the viruses in Coley's Toxin stimulates a massive production and response of the NK cells. When the treatment is successful, the NK cells function nonspecifically to also destroy the cancer cells.

More often, researchers and clinicians attempt to use the adaptive immune system against cancer. This is in part because mounting a massive innate immune responses usually comes at a huge cost to the patient (high fever etc.) and may, in some cases, cause patient mortality [16]. It is somewhat ironic that the clearest example of an immunotherapy success is one that induces a general immune response against bladder cancer [11].

When attempting to use the adaptive immune system against cancer there are basically three approaches that can be taken. The first approach is to correct the fact that the body seems to not be recognizing the cancer cells as malignant. The cells of the adaptive immune system responsible for this detection are the B lymphocytes and T lymphocytes (B and T cells). The B cells develop in the bone marrow and at maturity manufacture and present a unique antibody [6]. The antibodies recognize complementary antigens (generally surface proteins) on all cells. Those antibodies that recognize antigens naturally occurring on body cells are suppressed by regulatory T cells (T_{REG}) to avoid autoimmunity. The remaining antibodies and their presenting B cells are retained so that they can recognize substances foreign to the body. Since cancer seems to evade the detection of the antibodies, the idea is to supply artificial antibodies that are manufactured to recognize the surface proteins of the cancer cells [16]. This approach is more than theoretical. It has been recently demonstrated that the body can mount an immune response to cancer and that neoantigens (antigens produced by cancer cells but not by the natural body cells) do exist [8, 17]. Yet, this approach is not perfect, since cancer cells and their membrane proteins mutate quickly [8] and most tumors are heterogeneous.

The second means of using the adaptive immune system against cancer is through the use of what are called adjuvants [18]. These are compounds that boost the natural functioning of the various cells in the immune system. For example, B cells are partly stimulated by helper T cells ($CD4^+$ cells). B cells produce antibodies that tag malignant cells such that they can be destroyed by NK cells. One possible way of helping this process is by providing cytokines (proteins involved in immune cell signaling and regulation) or providing a chemical that promotes cytokine production [6]. The cytokines then stimulate the T and B cells which stimulate the NK cells, enhancing the fight against the cancer.

Another general approach to cancer immunotherapy is to destroy the signals emitted by cancer cells that inhibit immune response [14]. As noted above in the historical perspective, it has recently been better understood that cancer cells not only hide from the immune system through surface protein modulation but many in fact actively suppress immune response [19]. This is done when the cancer stimulates T_{REG} cells which accumulate in the environment immediately surrounding the tumor (cancer microenvironment), suppressing the activity of T and B cells [13]. How the cancer cells do this is not perfectly understood, but the cancer cells seem to be producing a number of signal proteins (transforming growth factor-β, interleukin-10m, and interleukin-35) that upregulate the production of T_{REG} cells. The immunotherapeutic approach is to either stop the upregulation of T_{REG} cells or stop their ability to suppress an immune response [15]. Removing the regulatory framework of the immune system has the inherent risk of accidentally producing general self-incompatibility in the patient and is therefore somewhat of a risk.

Tumor vaccines are either preventive vaccines that mainly

prevent infections with tumor causing viruses, or therapeutic vaccines. Tumor therapeutic vaccines are used to enhance the ability of the immune system to fight against an existing tumor or to initiate an immune response against tumor. Tumor therapeutic vaccines can also be preventative for tumor reoccurrence if they generate memory. The first FDA approved tumor vaccine (Sipuleucel-T) is based on isolation of dendritic cells from the patient blood and growing them with prostate antigen-cytokine fusion protein (PAP/ GM-CSF). In the culture, the dendritic cells which are antigen presenting cell are going to process the PAP antigen and present it on the class I and II Major Histocompatibility Complexes (MHC). The cytokines proteins activate the dendritic cells. The dendritic cells are then reinfused into the patient to activate $CD4^+$ and $CD8^+$ cells. When activated $CD8^+$ cell recognize the PAP antigen on the cancer cells they destroy the cancer cells and by inducing apoptosis. Activated CD4+ cells release costimulatory signals to the dendritic cells and to other immune cells to augment the immune response (Figure 2).

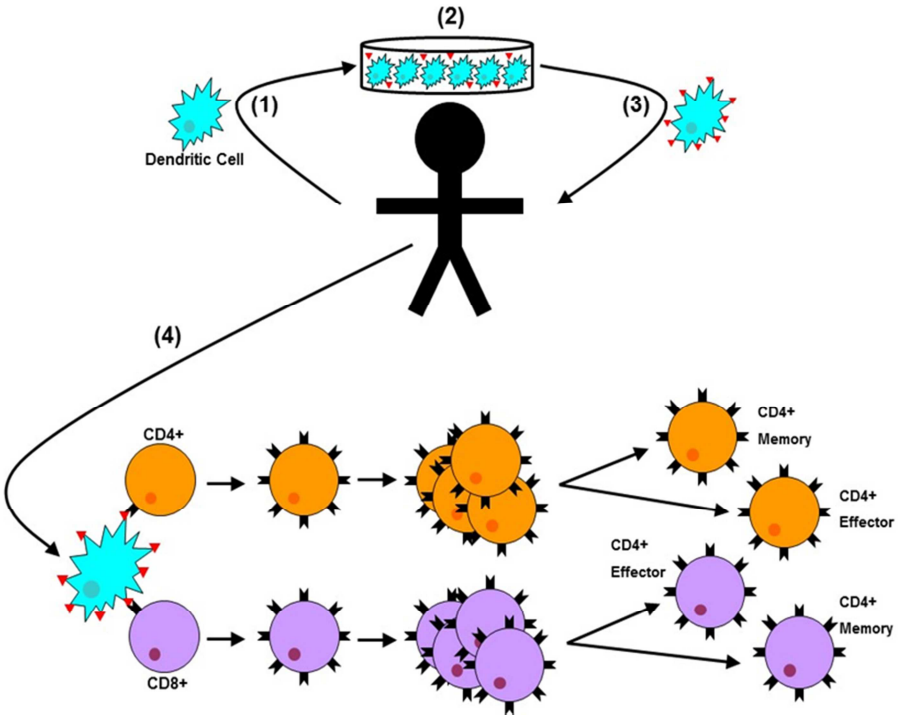

Figure 2. This figure explains the mechanism of action of the cancer therapeutic vaccine Sipuleucel-T. In step (1), dendritic cells are isolated from the blood of the patient. In step (2), these dendritic cells are grown with prostate antigen-cytokine fusion protein (PAP/GM-CSF). During this culture, the dendritic cells, which are antigen presenting cells, process the PAP antigen and present it on the cell surface using the class I and II Major Histocompatibility Complexes (MHC). In step (3), the dendritic cells are then re-injected into the patient. Once inside the patient (4), the dendritic cells activate CD4+ and CD8+ cells, which proliferate. The activated CD8+ cells will destroy cancer cells presenting the PAP antigen via apoptosis. The activated CD4+ cells release costimulatory signals to the dendritic cells and to other immune cells to augment the immune response. Both activated CD4+ and activated CD8+ cells differentiate into effector cells and memory cells. Modified, simplified, and adapted from [20].

3. Applications

As outlined above,"cancer immunotherapy" is best understood as an umbrella term for a variety of treatment types, all using the immune system in some way [17]. While it is theoretically possible to apply the principles of immunotherapy to any kind of cancer, in practice certain approaches have been applied to certain cancers. As a quick overview, it is often the case that CAR T cell therapy (chimeric antigen receptor T cell therapy) is used to treat leukemia [16, 21]. CAR T cell therapy functions by removing some of the cancer cells of the patient, identifying neoantigens, and then designing synthetic antibodies to match these neoantigens. These antibodies are injected such that the immune system of the patient can use them to fight the cancer.

Another kind of approach is through the inhibition of immune checkpoints [13]. This approach is often used to treat melanoma [22]. In this approach the PD-1 receptor on T cells is blocked. This receptor is ordinarily used by T_{REG} cells to inhibit autoimmune response (inhibiting B and T cells that are mistakenly attacking the body) but can also be used by cancer cells to repulse attacks by the immune system [17]. Inhibiting PD-1 receptor conjugation frees the immune system to attack the cancer because there is no way to downregulate the action of B and T cells [15].

A third approach is the general stimulation of the immune system through cytokines [23]. This approach is also used to treat melanoma, with the specific cytokine employed being

interleukins.

Current research looks to combine immunotherapy with other methods. One interesting approach has been the use of nanomaterials in conjunction with immunotherapy. Fan and Moon [24] outlined two such approaches. In the first approach, the immune system was used to enhance the effects of chemotherapy. Here, nanoparticles filled with a chemotherapeutic drug were bound to T cells. The T cells were already mounting an immune response to the cancer (in this case lymphoma) and in doing so they brought with them the particles of poison.

In the second approach, the goal was not to use immuno-specificity to deliver chemotherapeutic drugs but rather to provide the tools necessary to jump-start an immune response against the cancer cells (in this case melanoma). A nanoparticle was packaged with cancer-specific antibodies (in order to create more antigen presenting cells, thus triggering a specific immune response) and with an adjuvant (designed to induce the production of cytokines, thus amplifying the immune response once triggered). This nanoparticle was then targeted to the cancer microenvironment. The hope was to increase production of effective $CD4^+$ cells (helper T-cells) in the immediate vicinity of the cancer cells, thus making the immune response more targeted and effective [24].

Both of these approaches resulted in a longer lasting negative effect on cancer growth than less targeted approaches. There are two major advantages to immunotherapeutic approaches to cancer that incorporate nanotechnology. The first advantage is that such approaches target the cancer microenvironment specifically. This means that you can use less of the treatment, mitigating negative side effects on the patient.

The second major advantage to combining immunotherapy with nanomaterials is that you can also then combine immunotherapy with other cancer treatments such as chemotherapy. This enhances the effectiveness of chemotherapy immensely. It allows for much smaller doses of the poison, meaning less adverse health effects. Less chemotherapeutic drug in the system of the patient means you can also employ immunotherapeutic treatments simultaneously (adjuvants, inhibition of cancer immunoblocking, etc.). This is a big advantage because usually chemotherapy is so extreme that it destroys much of the immune system, making simultaneous immunotherapeutic treatment impossible.

Another approach for the development of tumor immunotherapeutic vaccine is to in vitro transfect tumor cells with the gene for the cytokine GM-CSF and reinfuse them into the patient. The transfected cells will produce GM-CSF that leads to activation of antigen presenting cells which activate CD4+ helper cells and cytotoxic T cells.

Using dendritic cells in combination with chemotherapy, Dr Ronald Levy and his colleagues in Stanford University developed a vaccine to treat lymphoma in an animal model [25]. In this approach, dendritic cells were injected into the site of the tumor, where they engulfed and processed antigens of dying tumor cells. To enhance the activation of the dendritic cells, they were accompanied with single stranded unmethylated CpG oligonucleotide that is recognized by a dendritic cell receptor called toll like receptor 9 (TLR9). The binding of CpG oligonucleotide to the TLR9 induced the expression of cytokines and other costimulatory signals for the immune cells. The dendritic cells presented the antigens to $CD8^+$ T cells which mediated systemic immune response against the cancer cells that carry the same antigen. In this approach, the dendritic cells must be customized for each patient to ensure MHC compatibility and prevent the patient's immune system from attacking the injected dendritic cells.

Another approach by the same group aims to eliminate the need for chemotherapy in the previous approach. In this approach, the patient's cancer specific T cells that are already available in the cancer tissue are activated using a monoclonal antibody that binds to OX40 receptor. The receptor is known as tumor necrosis factor receptor. In addition, a CpG oligonucleotide is used with assistance of other immune cells to amplify the expression of OX40 receptor in the target cells. The drug is administrated by direct injection into the cancer tissue.

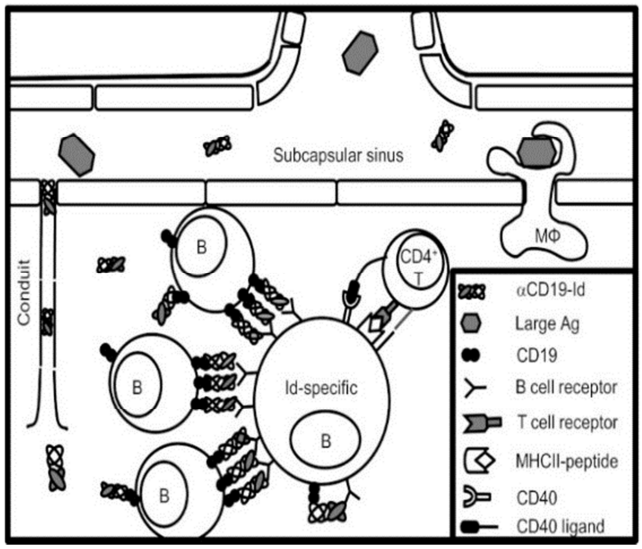

Figure 3. Proposed model: Id-specific B cells are stimulated by αCD19-Id targeted to CD19 on B cells in lymphoid follicles [25]. (reprinted with permission).

Dr. Ronald Levy group then designed a recombinant tumor vaccine to generate immune response to lymphoma. The vaccine is a diabody that is composed of anti B cell CD19 targeting moiety and a lymphoma id protein (αCD19-Id).

This vaccine can penetrate the lymph nodes and bind to noncognate B cells. Upon binding of αCD19-Id, the B cells will present the molecule to antigen specific B cells. Moreover, the vaccine can directly bind to the antigen specific B cells and colligate their CD19 molecules with and BCRs leading to synergistic activation of the specific B cells. In addition, the B cells can endocytose the id proteins and process them into peptides and present them to the $CD4^+$ T helper cells to activate them (Figure 3).

4. Regulatory Aspects

In many ways the regulatory aspects of cancer immunotherapy are not different from the regulations that would have to be followed in development and testing of any drug for any disease. Immunotherapeutic treatments for cancer must show themselves to be both effective and safe in culture, then in animal systems, then in humans in extremis, before being approved for use on humans generally.

The specific focus of regulation is on the identify, purity, viability, and potency of the treatment in question [26]. As trials progress, safety and efficacy of the drug are reviewed with more stringent standards such that he final product is safe to apply intravenously [26].

While the above sequence is the prudent course to follow when developing a medicine (due to just ethical concerns) there have been suggestions that it has hindered the development of immunotherapeutic drugs for cancer in ways that it has not hindered other approaches, such as chemotherapy. The scientific community has been particularly weary of immunotherapy because it has the theoretical possibility of becoming lethal very quickly and at very small doses [12], especially when it involves releasing the immune system from regulation (immune checkpoint inhibition). Thus, immunotherapy seems to get bogged down in early trials in humans because it is tried in circumstances where it is least effective. Early, clinical trials were permitted only on persons with large tumor loads whose health was otherwise highly compromised, and for whom death was imminent. Yet, studies have shown recently that immunotherapy is not effective when tumor loads are high [27]. Thus, studies focusing on terminal patients who have very high tumor loads probably underestimates the effectiveness of immunotherapy.

Finally, there are governmental regulations at the very early stages of testing that have made development of therapies difficult. These regulatory hurdles include long waits before studies are approved, but more importantly, the necessity to ensure high safety standards at even very early stages of testing. For example, it was the case in Europe that even in the first stages of testing with animal subjects, the therapy already needed to be food-grade quality. This adds substantial time and costs in testing and development for drugs that may prove ineffective [18].

5. Future Directions

The future of immunotherapy is complicated. The research done over the past century seems to indicate that it is not the "silver bullet" treatment that it has been portrayed to be. Studies indicate that response to the treatment is highly specific to patient, with some patients having miraculous recoveries and others showing no improvement [9]. Moreover, it has proved difficult to identify those individuals who will benefit from the treatment and those who will not. A worthy question is - what are the biomarkers that tell us who will benefit and who will not? [13, 18]. There are some general trends in this regard, however. Patients who responded to immunotherapy were generally those in early stages of their cancers. Specifically, patients that responded well to treatment had low tumor loads at the time treatment was begun [27]. Moreover, treatments were most effective when they were localized and sustained [13]. A general stimulation of the immune system in the hopes that the cancer will be destroyed in the immune system storm that follows is generally not a successful treatment.

This points to two major ways forward. In the first case, an investment should be made in trying to identify biomarkers that indicate which patients are the most successful candidates for immunotherapy. This will require an investment in better understanding the surface proteins of cancer cells, in order to look for universal neoantigens (a few of which have been discovered, but not many) [3]. Second, it is important to establish novel ways of producing a sustained and highly localized immune response at the site of the tumor [24, 28].

Second, since immunotherapy seems, like other treatments, only a partial approach to cancer, it is important to find ways to combine immunotherapeutic approaches with other more conventional approaches to cancer (chemotherapy and surgery). Recent development of using gene editing technique of CRISPR in immunotherapy may become a successful approach for many different cancers.

Finally, perhaps the biggest concern with immunotherapy as a general medical technique is the possibility that the treatment will provoke a localized or general autoimmune reaction. Such a reaction could become fatal very quickly and may not be able to be reversed. In this respect, workers in cancer immunotherapy have begun to collaborate with workers in rheumatoid arthritis, who have been dealing with problems of autoimmunity for many years [5]. The problem of autoimmunity is one that needs to be circumvented before

we can be confident that immune checkpoint inhibition is a safe and viable way forward.

6. Conclusion

The advent of immunotherapy for cancer treatment bodes huge hope in the war on cancer treatment battles which often results in favor of cancer. Though, it remains a long way to treat many different kinds of cancers especially hard to tread solid tumors using immunotherapy, the rapid development in this area is encouraging. We would like to end this review with a conjecture yet to tested experimentally. Considering that the cancer arises by accumulating mutations in the genome and inherent occasional mistakes of DNA polymerase during cell division is one of the leading mechanisms, along with environmental stresses, to develop mutations in the DNA. Billions of cells undergo cell divisions and older people with more cell divisions may accumulate more mutations. It is tempting to speculate that every human has in their life-time cancerous cells that are being fought constantly by their own immunity mechanism. It is this constant warfare between the cancerous cells and immune system where the winner determines whether one will have cancer or not. By disguising, using various cellular mechanisms, the cancer cell try to evade the immune system but by learning or retooling immune system to fight those disguises may one day tilt the warfare towards the immune system- a day when the pioneers of immunotherapy research will be remembered in the cancer fighting history book.

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