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Immunotherapy and Vaccination as Cancer Treatments

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Abstract

Cancer can eventually develop randomly in anyone at any age. However, characteristic to most cancer cases is a loss of identity in the affected cells. At the birth of each cell, the cell is recognized as "self" by the body's defense against illness- the immune system. However, if cells develop into a cancer cell line in their lifetime, they ultimately lose their "self-ness" and begin to develop new proteins, now known as novel antigens, that are no longer seen as "self" by the body. This feature makes cancer cells an optimal target for treatment via elimination by the immune system. By arming and modulating the immune system through immunotherapy, it is possible to assist the immune system in the elimination and prevention of cancer. In this review, we will discuss all the current viable treatments of cancer, and why immunotherapy and vaccination maybe our best bets for future prevention and treatment.

The Overview of Cancer Genesis

Cancer is classified by abnormal cell growth outside the means of cellular regulation. Within the normal lifecycle of cells, there are strictly regulated events regarding cellular reproduction. Normal cell division results in two healthy daughter cells each being identical to the original. When we examine fertilization, we have specialized cell divisions, where one cell becomes a series of specialized cells, and each of these cells goes on to makeup the trillions of cells we have in the body. Though in cancer, mutations to the genes or their regulatory DNA can cause needless and uncontrollable replication, and ultimately a loss of identity and specialization for this cell and all its daughter cells. These rogue cells are now rapidly growing, growth factor independent, immortal, and ever changing.

Several hundreds of genes within the human genome control the regulation of the cell cycle and cellular growth. Given the number of genes within each cell, and given the number of cells within the human body, and then on top of that the amount of carcinogens humans are exposed to throughout their lifetime-it's pretty clear to see that the odds of one developing cancer within their lifetime are not that slim. In fact, according to the US National Cancer Institute SEER Cancer Statistics, a person's chance of developing cancer at some point in their lifetime is about 43% of all men and women [1]. Of all these people developing the disease, only about half will die from the cancer. In 2012 in the US alone, an estimated 14 million people were living with cancer [2]. However, to clarify, this is only about 4% of the US population. The treatment outcomes vary amongst cancer cases, and this may be linked to the cause of the cancer and the affected tissues.

The following are some of the different ways cancer can develop within the body:

Random Mutation

About two-thirds of all cancers in adults can be attributed to random mutations [3]. A person can live a relatively healthy lifestyle, never be exposed to any risk factors, and yet still develop cancer. Every second, numerous cells within the body are preparing to undergo cell division by replicating DNA. Considering the number of cells and the size of the human genome, every second there are random errors within the replicating genome. DNA replication is not a perfect process, and the chance of an error occurring is 1 out of 100 million. Fortunately, special repair enzymes are able to fix almost all errors during or after replication, reducing the rate of error to about 1 in 10 billion base pairs [4]. As the human genome has about 3 billion base pairs, which means about 1 error in every 3 cells that undergo replication. Within a generation of the human species, scientists expect about 30-50 mutations to stick within the genome [5], causing further diversity among the future generations. Although random mutation may play the largest role, some highly linked carcinogens have been implicated to also play critical roles in cancer development [3].

Carcinogen Influence

Although random mutation accounts for about two-thirds of cancers, there are still risk

factors that are strongly linked to certain types of cancers, such as tobacco products to lung cancers [6] and prolonged sun exposure to skin cancers [7]. Several radioactive substances, such as gamma or alpha rays, are known to be carcinogenic due to their damage to the DNA. Other substances, such as tobacco, asbestos, and dioxins, have chemicals that interact with the DNA structure and at high enough doses or prolonged exposure, can eventually cause cancer.

Genetics

Although most cancers are sporadic, there is a selection of hereditary cancers (only about 5-10% of cases) [8]. Some notable and more prevalent examples are the BRCA gene in the case of breast cancer and familial types of colon cancers. Inherited mutations in the BRCA1 or BRCA2 genes increase the risk of breast and ovarian cancers to 75-80% [9]. There is also the genetic risk of hereditary nonpolyposis colorectal cancer, where people have an 80% lifetime risk of developing colon cancer [10]. Although genetics is a popular field of research in terms of cancer, not many cases of genetics are currently known. In all colorectal cancer cases, only 3% are considered familial. Similarly, incase of breast cancer, only 5-10% are attributed to hereditary factors.

Viral and Other Microorganism

It is approximated that 18-20% of deaths caused by cancer worldwide are initiated by a viral or bacterial infection [11]. Two most notable cases are the Human Papilloma Virus (HPV) in the cause of cervical and throat cancers, prompting the creation and promotion of vaccination, and the other being the H. pylori bacteria in the cause of stomach and esophageal cancers. Both of these cancers can be reduced to near elimination; papilloma can be prevented through vaccination and screenings, and H. pylori can be treated with antibiotics.

Certain populations are more vulnerable to these types of changes than others. For example, the elderly are more susceptible to developing cancers since about 77% of all cancer cases are diagnosed in people over the age of 55 [12]. What's intimidating about this statistic isn't the high percentage, but the fact that this age grouping (people over 55) is expected to double within the US by the year 2060 [13]. A higher elderly population will yield more newly diagnosed cases of cancer. According to the CDC, seniors now have an average life expectancy of 79 years of age. To clarify why the general population thinks we are seeing more and more cancer cases, in 1950, life expectancy was 68 years of age. In 1975, it was 73 years of age. In 2000, it was 76 years of age [14]. If we keep going along the same trends of advancing life expectancy, we can expect the norm of people to live well into their 80s or even their 90s through the latter half of the 21st century. Although that is an optimistic outlook, this ultimately means more cancer cases, and proper preparation is needed to deal with that on a global scale.

Another population more susceptible to developing cancer includes people who are considered obese. As a country embattled with obesity, a lack of the proper diet and exercise is a problem for many Americans. The American Society of Clinical Oncology (ASCO) warned that soon obesity would pass tobacco as the number one threat in the United States for cause of cancer. A higher body weight is accompanied by higher levels of hormones and cell signals. These in turn tell cells to divide more often, increasing the chance of random mutation to occur, and the tissues that divide most often, like the colon, will be affected the most. In association is the increase in food intake, which is correlated with higher levels of carcinogens in food waste. The increase in body fat and weight has been linked to a number of different cancers, including, colon, breast, rectal, esophageal, pancreatic, kidney, thyroid, and gallbladder cancers [15,16].

Current Treatments in Cancer

Many treatments are currently available for cancer patients, and the ones most commonly undertaken are surgery, chemotherapy, targeted radiation, and in some specific cases, hormone therapy, immunotherapy, and stem cell treatment.

Surgery is the primary option for treatment; however, in cases where the tumor location may be difficult or impossible to reach, or due to the extension of the cancer, other options such as rounds of chemotherapy and radiation are elected. Radiation works by using low- and high-energy x-rays to cause damage to the cancer cell DNA to the point of initiating cell death. To bypass the skin and other surfaces above the tumor, the radiation is usually administered in split beams, which intersect at the cancer to administer a larger dose of radiation. In many cases, the negative side effects of radiation can be felt. The other main option, usually used in combination with radiation, is chemotherapy. This is where cytotoxic, chemotherapeutic agents are used, and these are generally DNA alkylating or antimetabolite agents, killing all rapidly dividing cells, such as hair cells (causing hair loss) and digestive tract and stomach cells (causing nausea and vomiting). There is also targeted chemotherapy, which use physiological modification in specific cancers. For example, blocking the estrogen receptors in breast cancer can help to inhibit cell growth [17]. Others are Bcr-Abl inhibitors, which help treat Chronic Myelogenous Leukemia (CML) [18]. In both these treatments, there are numerous negative side effects that in the end up hurting or in some cases killing patients, and in many cases the patients elect to forgo treatment rather than succumb themselves to living out their final moments in chronic sickness.

Here, patients may undertake alternative treatments, such as stem cell treatment and immunotherapy. Stem cell treatments are mostly used for cancers of the blood, such as leukemia, lymphoma, and myelomas. These cancers occur when the precursors to these blood cells become mutated, and then go on to produce mutated cells very rapidly. The idea behind stem cell transplantation is to switch out these cells in the bone marrow for new, functional stem cells. Other types of stem cell treatment play on the role of the immune system in cancers. By adding stem cells that promote "anti-cancer" immune responses, they can increase these cell populations, which will then go on to target the cancer. This is also considered a type of immunotherapy.

Immunotherapy is any treatment that aims to modify, dampen, or enhance the immune system to cure a disease or to alleviate an illness. These treatments can be active or passive, meaning that they can help to activate certain T or B cells to fight the cancer and have the body do the work, or we can use already made products to momentarily treat the cancer, and these products or usually antibodies or immune factors that help to promote a passive immune response. Ultimately, both of these methods exploit the fact that cancer cells are subtly different from normal human cells, and that these cells carry cancer antigens [19,20]. By priming the immune system against these subtle

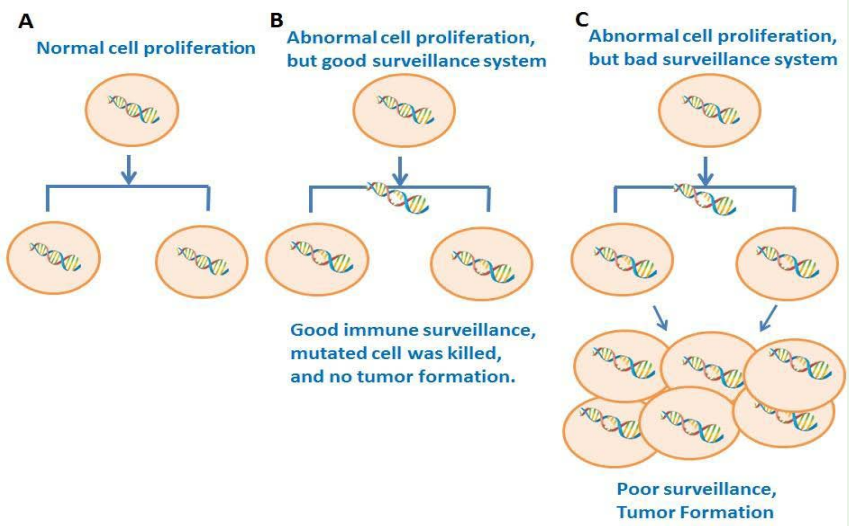

Figure 1: The process shown is a depiction of what roles immune surveillance play and what it can accomplish under the burden of tumor cells. In Figure 1A, we have normal cell proliferation into two daughter cells. In Figure 1B, there is a mutation in cell division, and both daughter cells now carry this mutation creating oncogenes. These mutated cells were picked up through immune surveillance and underwent apoptosis. In Figure 1C, with a poor immune system, as is the case with the elderly, and the immunocompromised, the tumor cells went undetected and allowed to proliferate exponentially.

differences, the immune system should be the overseer in the rest of the destruction of the cancer itself (Figure 1). One way to possibly do this, although tricky, is to vaccinate the body against its former self, also known as a cancer vaccine.

What is a Cancer Vaccine?

As stated before, as tumor cells develop they lose a part of themselves and their cell line diversity. They either express mutated proteins, or will go on to express too much or too little of a specific protein. These changes to the cell surface are known as cancer or tumor specific antigens. Tumor antigens can be used as immunogens to generate cancer specific therapies if immune tolerance can be broken, a process that normally prevents the immune system from attacking any cells it identifies as self. As immune cells develop, they are exposed to a number of self-proteins to develop tolerance. Thus, any protein recognized as a foreign intruder to the immune system can trigger immune response, including proteins present in either small or large amounts (Figure 2).

There are two types of tumor antigens: those that are Tumor-Specific (TSA) and those that are Tumor-Associated (TAA). TSA antigens are known only to appear on tumor cells and not at all on the normal cells of the body, examples include mutated ras and p53

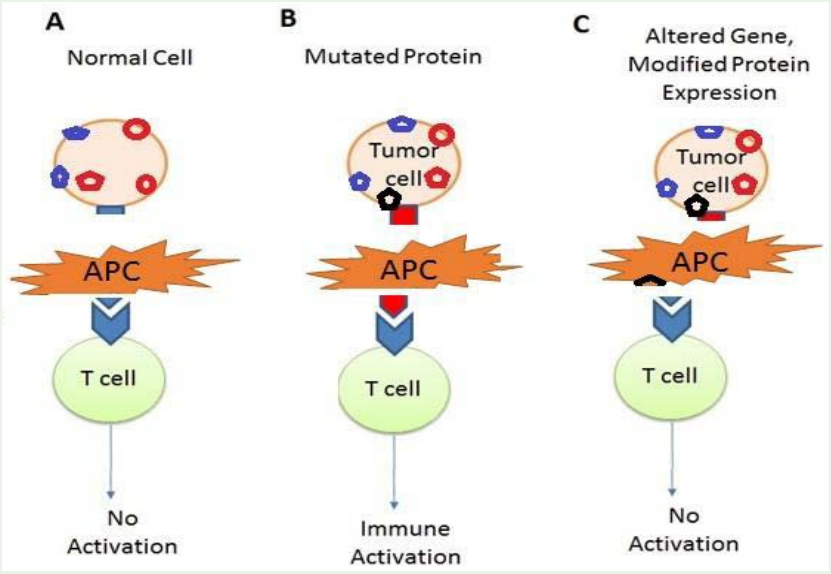

Figure 2: Shown are scenarios, compared to normal (2A), where mutated proteins (2B) or protein expression (2C) can play roles in the activation of the immune system in tumor suppression. The blue coloration represents self, where black is non-self. In Figure 2A, the result of the T-cell interaction is tolerance and no immune activation. However, in Figures 2B and 2C, both cases result in phagocytosis by APC cell, but 2B shows activation of the immune system due to functional T cell, and 2C shows no activation (anergy) due to the impaired immune system though there is antigen presentation.

Table 1: Common Tumor Antigens and their Associated Cancers.

Name	Cancer Type
MUC-1	Breast, Pancreatic, Colon Tumor [37]
Epithelial Tumor Antigen (ETA)	Breast Tumor [38]
CA-125	Ovarian/Cervical Tumor [39]
MZ2-E	Melanoma Tumor [40]
NY-ESO-1	Multiple Myeloma Tumor [41]
HER2	Breast, Ovary, Lung, Pancreas, Prostate, Colon Tumors [42]
Thyroglobulin	Differentiated Thyroid Cancer (DTC)[43]
HE4	Ovarian and Endometrial [44]
Neuron-specific enolase (NSE)	Small cell lung cancer (SCLC) [45]

genes. However, TAA's are both on tumor cells and also on some normal cells in the body. A list of some examples of both is displayed in Table 1.

A unique method to prime the immune system against these antigens is vaccination. There are vaccinations that prevent cancer, like Gardasil, Cervarix, and the Hepatitis B Vaccine. These are to prevent infection via the viral strains that are associated with each of their cancers. Vaccines for cancer treatment are designed to boost the immune system to target the cancer cells, and only the cancer cells, by utilizing cancer-specific antigens. The immune activation is designed to target only cancer cells, so side effects normally seen in radiation and chemotherapy will not occur. Also, with the development of immune memory long after the cancer is gone, it would be unlikely that the cancer would reappear after treatment with an effective cancer vaccination.

At the moment, most cancer vaccinations for treatment are still undergoing clinical trials. However, one such vaccine, called sipuleucel-T (Provenge), has been FDA approved for metastatic prostate cancer [21,22]. The vaccination is person-specific, as it uses the patient's own white blood cells as the key component. The patient's blood is drawn and the white cells are taught to identify the cancer outside the body, most notably by Antigen Presenting Cells (APCs) such as Dendritic Cells (DCs). The cells are then reinjected into the patient, similar to a blood transfusion, where they prime the rest of the immune cells to destroy the cancer. This method is widely being undertaken in current cancer research, as it is an efficient way to prime the immune system to identify all types of cancers and even in other, now incurable, diseases [23-26]. Vaccinations for bladder [27], brain [28], breast [29], cervical [30], colorectal [31], leukemia [32], myeloma [33], pancreatic [34], prostate [35], kidney, lung, and melanoma [36] cancers are currently undergoing clinical trials and affected patients are encouraged to enroll in order to get a better understanding of future treatments..

Future of Cancer Vaccines

Although cancer vaccination is a promising idea, and may be the future of personalized cancer treatment, it has its limitations. To develop better, more effective cancer vaccines, we need to conduct further research to overcome barriers and progress in the field.

One such barrier to be overcome through future research is the suppression of the immune system by the cancer cell lines, especially at the site of the tumor. The microenvironment created by the tumor cells at the site of the cancer is usually inhospitable for T-cells and other immune cells trying to infiltrate the tumor. Tumors are known to suppress inflammation so that there isn't proper activation by the immune system [46]. Also, immune systems of the immunocompromised and elderly are usually hindered with poor immunosurveillance. With weakened or dampened responses, the vaccine might not be as effective in these populations. To overcome these factors, new adjuvants need to be developed to increase the efficacy of the vaccines and cause a stronger activation of the immune system by enhancing the antigen-specific immune response [47]. Some studies currently are testing the use of poly (I:C), a synthetic immune warning signal, in the use of vaccination to help promote the immune response [48]. Here, in the animal model, these signals helped to decrease the size of the tumor and promote an anti-tumor immune response. Other studies are using pre-activated antigen presenting cells, such as dendritic cells, to help activate other T-cells and B-cells [49-51].

Another obstacle in the efficacious development of cancer vaccines is the process of development and breaking of immune tolerance. Cancer cells may still appear normal to the body, even though their DNA demonstrates otherwise. Better methods need to be devised to break the immune tolerance with these certain cells. However, accomplishing this break in immune tolerance increases the risk of causing an autoimmune response to normal, healthy cells. Current studies are overcoming the case of immune tolerance in order to promote safe activation of the immune system against cancers showing self-antigens [52-54].

Other obstacles include the management of the size and location of the tumor. Although the immune system is relatively effective in immediate and preventative treatment, it has difficulty eliminating large tumors. To tackle this problem, better ways of tumor infiltration need to be developed, although we need to keep in mind the massive inflammation activated at tumors of large size and the damage this process can leave behind. Tumor location can also be an interesting challenge, as those residing in the brain are often immune-privileged, and we have yet to develop completely safe neurological vaccines for human treatment. Although, this can be overcome by use of combinational treatment with others, such as surgery, chemotherapy or radiation [55]. With the use of other treatments, these can help to break up the large tumor and its environment by killing some of the tissue, so that the immune system can help clear the dead tissue and become properly activated for the clearance of the rest of the tumor.

Conclusion

Although common cancer treatments such as surgery, chemotherapy, and radiation are useful and are first line treatments at this time, each is accompanied by side effects and may become less common forms of treatment in the years to come. Viable options such as immunotherapy and vaccines are coming to light as prospective leaders in cancer therapy. As we learn more about the mechanisms and intricacies of the interaction between the immune system and cancer, better, personalized treatment vaccines should become available within the next 10 years for wide use by patients.

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