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Treating Cancer: Vaccines Aiding the Human Immune Response

Introduction

Cancer is one of the most devastating diseases in the world today. Despite the efforts of modern medicine, cancer rates continue to rise. Globally, there were 8 million deaths from cancer in 2012. In 2016 in the United States alone there were five hundred thousand cancer related deaths (Hosick *et al.* 2017). Cancer's remarkable ability to avoid the body's immune responses this is the chief reason its cure has been so elusive. This paper will provide some background information on cancer and how it is able to effectively evade the immune response. It will also discuss some of the different cell types involved in immune responses to cancer. Lastly, recent research papers investigating new developments in cancer treatment and the mechanisms of dendritic cell (DC) vaccines and the initiation of cancer immune responses will be discussed.

Understanding Cancer

Cancer can be defined as uncontrollable cell growth within a specialized tissue of the body which affects cell and organ function. In serious cases, cancer can travel through the blood and lymphatic vessels, affecting other areas of the body besides the initial site. Although they may not be fully understood, there are many causes of cancer, including viruses, genetic, environmental, and lifestyle factors (Hosick *et al.* 2017).

Genetic mutations lead to the start of cancer. These mutations limit growth control and are known as malignant transformations. An oncogene is one of the hundreds of genes that mutates or malfunctions in cancer, dysregulating cellular division. These genetic mutations often are caused by chemicals known as carcinogens, many kinds of radiation, and different kinds of viruses. They can also be caused by genetic mistakes during DNA replication (Hosick *et al.* 2017). Cancer cells have many

unique traits that separate them from other cells. Apposed to cancer cells, normal cells generally grow in a single layer in culture. In contrast, cancer cells exhibit uncontrolled growth, typically multiplying until they eventually pile up forming a tumor. There are two types of tumors; benign and malignant. Benign tumors are essentially harmless and do not invade other parts of the body. Malignant tumors invade other parts of the body and are difficult to eradicate (Hosick *et al.* 2017). Interestingly, cancer cells are often unaffected by hormones and growth factors, and, are essentially immortal in that they can replicate an unlimited number of times. Another unique trait of cancer cells is that in late stages, cancer cells are easily recognized because they change in shape and size. This alteration of shape is the primary means by which different types of cancer are identified (Hosick *et al.* 2017).

Treatment

The most common cancer treatments are chemotherapy, radiation therapy, and surgery. Chemotherapy involves taking a variety of drugs that combat cancer cells, usually requiring multiple treatments. These drugs often kill normal cells as well as cancer cells. Radiation therapy uses high-energy radiation that kills cancer cells by causing DNA damage. Surgical removal of tumors is generally performed in early stages of cancer, preventing further cancer growth (Ruiz-Ceja and Chirino 2017).

Cancer vaccines are less common but can be developed; unfortunately, they are often ineffective. This is primarily due to mechanisms that suppress T cells and other antigen presenting cells (Saxena and Bhardwaj 2017). There are, however, many new therapies being developed to treat cancers. These new developments often result from the understanding that most cancers express antigens that can be recognized by T cells (Woo *et al.* 2015).

Role of T cells

As seen in figure 1, T cells are normally effective in destroying cancer cells. Although many cancer patients exhibit endogenous expansion of CD8 T cells and antibodies that are specific to tumor

antigens, progression of cancer is often unaffected. This suggests cancerous cells can escape the immune response. Despite the importance of CD8 T cells, there are quite a few other types of T cells that are significant in the immune response to cancer, including Natural Killer T cells and γδ T cells (Woo *et al.* 2015).

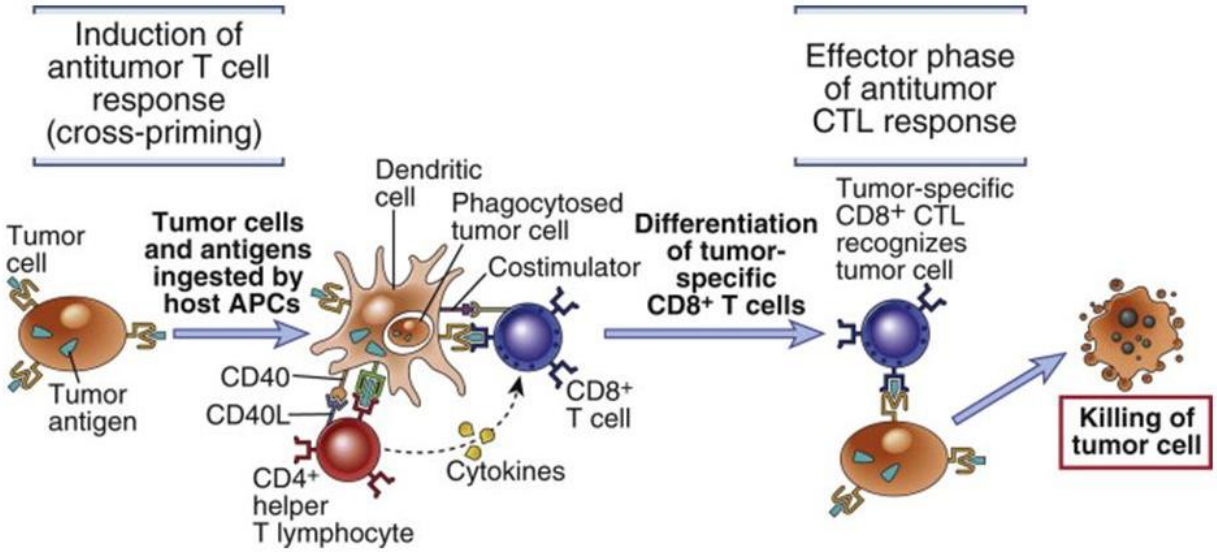


Figure 1. Antigen presenting cell ingesting a tumor cell and presenting to T cells, tumor specific CD8 CTLs kill tumor cells (Abbas *et al.* 2014)

Most of the research today examines the tumor microenvironment; this is the site where antigens are originally captured and where antigen-presenting cells, including DCs, are activated. The tumor microenvironment is also the site where activated T cells carry out the final stages of tumor elimination (Woo *et al.* 2015).

Natural Killer T Cells (NKT Cells)

NKT cells play a significant role in tumor immune surveillance There are two major types of NKT cells, type I and type II. Both type I and II NKT cells are CD1d-restricted. Type I NKT cells can recognize glycolipid antigens presented on CD1d molecules. Type II NKT cells have immunoregulatory functions

and can recognize more antigens than type I NKT cells. This is due to their increased variability of T cell receptors. NKT cells can be activated by antigens from bacteria, glycolipid antigens presented by CD1d molecules, or from tumor-derived ligands, particularly ganglioside GD3 and endogenous antigen iGb3 (Woo *et al.* 2015).

Once activated by CD1d-presented antigens, type I NKT cells begin to produce many cytokines and become cytotoxic. They can also induce upregulation of costimulatory molecules on dendritic cells and macrophages that promote T cell activation. The type I NKT cells seem to have a large role in immune responses to cancer as they produce cytokines that coordinate the activation of both natural killer cells and CD8 T cells. Because of this, type I NKT cells could potentially be used in cancer immunotherapy.

Type II NKT cells differ from type I NKT cells in that they are involved in regulation of immune responses rather than induction of them and they do not have a role in cancer immunity. Immune responses are regulated by production of Interleukin-13 and activation of signal transducer and activator of transcription 6 (STAT6) pathways (Woo *et al.* 2015).

γδ T Cells

Antitumor immune responses may involve γδ T cells. Experiments have shown that γδ T cell deficiency often leads to increased occurrence of tumor development. Although some antigen presenting molecules are unknown, it has been identified that γδ T cells recognize many molecules that are expressed by cancer cells or associated with them. There are several tumor-killing mechanisms that involve γδ T cells because they can express cytotoxic granules, produce effector cytokines, and can facilitate antibody-dependent cellular cytotoxicity. In addition to this, γδ T cells can activate DCs and interact with CD8 T cells and natural killer cells to regulate their proliferation (Woo *et al.* 2015).

Unfortunately, γδ T cells are not fully understood. γδ T cells exhibit anti-tumor activity in the tumor microenvironment, however, their proliferation and cytotoxic activity is inhibited by regulatory T cells. Other immune suppressive factors such as TGF-β, PGE2, IDO, and soluble NKG2D ligands inhibit antitumor activity of γδ T cells. In most cases, γδ T cells stimulate antitumor immune responses, but, in some types of cancer they have been observed to suppress T cells (Woo *et al.* 2015).

Role of DCs

The primary role of DCs is to present antigens and co-stimulatory signals to T cells of the adaptive immune system. Immature DCs are good at capturing antigens but have poor secretion of cytokines and expression of costimulatory molecules. Activated DCs capture less antigen but express more costimulatory molecules and have a heightened ability to produce cytokines (Veglia and Gabrilovich 2017). Activated DCs also exhibit an increased expression of major histocompatibility complex (MHC) class II and C-C receptor type 7 (chemokine receptor); due to the increased presence of this receptor, activated DCs actively migrate to lymph nodes. Because of these features, mature DCs are good at inducing T cell responses (Veglia and Gabrilovich 2017).

DCs play a significant role in cancer treatments because they can initiate both innate and adaptive immune responses. Tumor-associated DCs are, for the most part, functionally defective (Veglia and Gabrilovich 2017). These DCs develop a regulatory phenotype. This is most likely due to the presence of immunosuppressive mediators in the tumor microenvironment (Woo *et al.* 2015). All tumor vaccines target DCs, which have a high capacity for initiating innate and adaptive immune responses; thus, they are frequently dubbed natural adjuvants. This is important because cancer vaccines require adjuvants to be effective. (Saxena and Bhardwaj 2017).

Tumor antigens can be recognized by CD141 DCs. These DCs are particularly important in vaccine development because they activate CD8 cytotoxic T lymphocytes (CTLs) which are tumor

specific. The CD141 DCs activate CD8 CTLs through a cross-presentation pathway (Saxena and Bhardwaj 2017). Cross presentation is essential for the activation of CD8 T cells. It is mainly carried out by DCs.

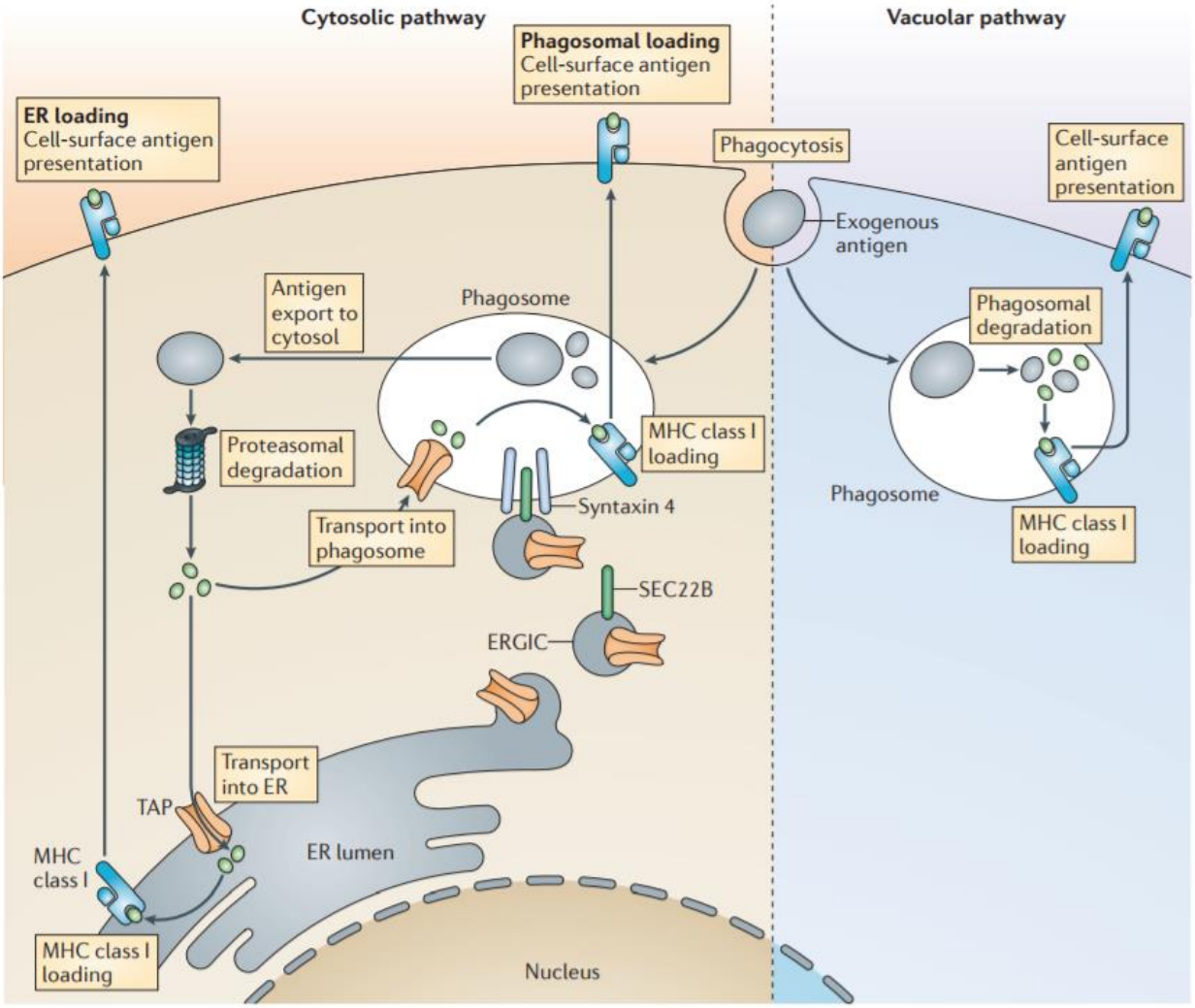


Figure 2. Intracellular cross-presentation pathways leading to antigen presentation to T cells (Joffre *et al.* 2014)

Cross-presentation is the process by which antigens are broken down and loaded onto MHCs (figure 2). These loaded MHCs are then transported to the cell surface and presented to T cells. There are two important pathways of intracellular cross-presentation, the cytosolic and vacuolar pathways (Joffre *et al.* 2012). The cytosolic pathway begins with the degradation of proteins in the cytosol by the proteasome into peptides. The peptides are then moved to the endoplasmic reticulum by TAP

transporters where they are loaded onto class I MHC molecules. The class I MHC then moves to the cell surface for presentation (Joffre *et al.* 2012). The vacuolar pathway is more simplistic as antigen processing and loading onto class I MHCs occur in the phagosome then the MHC moves from the phagosome to the cell surface for presentation (Joffre *et al.* 2012).

DC Dysfunction

Although DCs are present in tumor microenvironments, cross-presentation mechanisms of DCs in tumor microenvironments are often limited. Since activation and differentiation usually fail in tumor associated DCs, it is believed that DC dysfunction is a large contributor to the unresponsiveness of the immune system in cancer (Veglia and Gabrilovich 2017). There are numerous causes of DC dysfunction, including hypoxia, accumulation of adenosine, increased levels of lactate, and decreased pH; all of which tend to be associated with the tumor microenvironment. Also, the presence of Interleukin-10 can lead to DC dysfunction by inhibiting Interleukin-12 production by tumor infiltrating DCs, thus hindering their ability to initiate antigen-specific T cell responses. Interleukin-10 is produced by a variety of cells including T helper cells and tumor associated macrophages. Inhibitory molecules, such as PD-L1, are also known to cause DC dysfunction (Veglia and Gabrilovich 2017).

Cross-presentation is often impaired, which frequently leads to the activation and maintenance of anti-tumor immunity becoming altered. One of the major factors that leads to the impairment of cross-presentation is the accumulation of lipids in DCs. Many different recent studies have shown that lipid accumulation in DCs is usually caused by endoplasmic reticulum stress. Lipid accumulation in the endoplasmic reticulum impairs the process of peptide loading of class I MHCs, this makes the DC unable to activate T cells (Veglia and Gabrilovich 2017).

Tumor-infiltrating DCs

Tumor-infiltrating DCs may play a role in how cancer avoids immune responses. It has recently been discovered that tumors can convert infiltrating DCs into regulatory cells which suppresses immune responses. This occurs when AT-rich sequence-binding protein 1 is expressed by tumor cells, which converts DCs, making them high producers of Interleukin-6 and galectin-1. Once these DCs are converted, they both promote tumor progression by secreting Interleukin-6 and suppress the immune system by secreting galectin-1. In these DCs, genes that regulate immune suppressive functions are overexpressed and a gene that prevents maturation of DCs called STAT3 is turned on. The STAT3 gene leads to decreased responsiveness of DCs to danger signals (Veglia and Gabrilovich 2017).

Tumor-Associated Antigens (TAAs)

There are many different types of antigens that are expressed by tumorigenic cells. TAAs, which are different from tumor-specific antigens (TSAs), are divided into many different categories. TAAs are found on most cells but are most prevalent on tumor cells while TSAs are found only on tumor cells. Different TAAs need to be treated in different ways (Saxena and Bhardwaj 2017).

One example of a TAA is the Cancer testis antigen, which is generally found on cells in the germ line. They are, however, found in many tumors. Treatment of tumors that produce cancer testis antigens includes peptide, cell based, RNA, and DNA vaccines. These vaccines may be used in conjunction with virotherapy and chemotherapy (Saxena and Bhardwaj 2017).

The viruses that cause tumorigenic transformation produce oncoviral antigens. These antigens are recognized by the immune system as “non-self” because they are present on infected cells. These antigens are tumor-specific (Saxena and Bhardwaj 2017).

Neoantigens, which are MHC restricted antigens, are produced by mutations in tumor cells so they are not found on all tumors. Because neoantigens are unique to the individual, vaccines that target these antigens need to be personalized (Saxena and Bhardwaj 2017).

Finally, antigens that are over expressed significantly in tumor cells compared to normal cells are simply known as overexpressed antigens (Saxena and Bhardwaj 2017). The study of TAAs is an important aspect of cancer research as they play a significant role in cancer vaccines. In addition to TAAs, adjuvants are also vital in effective cancer vaccinations.

Adjuvants in Vaccines

Adjuvants are defined as substances that can boost the immune response to an antigen. They provide the ideal conditions for processing and presentation of antigens from antigen presenting cells to T cells. Appropriate adjuvants are necessary to get the best immune response from a vaccine (Benvenuto 2009). They are extremely important in cancer vaccines because they can help to bring the vaccine contents to the lymph nodes. Currently, it is believed that successful vaccines need adjuvants that activate cross-presenting DCs (Saxena and Bhardwaj 2017). Unfortunately, adjuvants often come with adverse side effects. Hence, many different adjuvants are used to find a balance of immunogenicity and a low level of adverse reactions (Benvenuto 2009).

Conventional Adjuvants

Aluminum-based salts were the first adjuvant used in human vaccination. They enhance the immune response by acting as a depot formulation for antigens, absorbing then slowly releasing them (Benvenuto 2009). This improves antigen uptake by presenting cells, in particular, T helper 2 cells. The use of Aluminum salts in cancer vaccines is questioned because of a pre-disposition of causing pro-tumorigenic differentiation of T helper cells, while the activation of cytotoxic T cells is the most important factor in immune responses to cancer (Saxena and Bhardwaj 2017). Aluminum salts are the most widely used adjuvants in vaccines (Benvenuto 2009).

Incomplete Freund's adjuvant and Montantide adjuvants facilitate slow release of antigens by concentrating vaccines at the injection site. The downside of these adjuvants is that vaccine deposition

may lead to T cell depletion. However, this can be prevented when vaccines containing these adjuvants are combined with synthetic long peptides and additional activating adjuvants (Saxena and Bhardwaj 2017).

TLR agonists can also be effective adjuvants. They improve the immune response by activating and maturing DCs thus enhancing the T cell response. Synthetic TLR agonists are used broadly in the clinical setting. There are many different types of TLR agonists that are effective in vaccines, including derivatives of synthetic TLR3 ligand, TLR2, TLR7 ligand, and TLR9 agonist. Mixtures of TLR agonists are usually included in vaccines as this maximizes DC activation and maturation (Saxena and Bhardwaj 2017).

New Adjuvants

Nanoparticles are a recently developed type of adjuvant that help vaccines access the lymph nodes. These nanoparticles can allow the vaccine to be directly deposited into the lymph node via intranodal injections, activating DCs and CTLs. Nanoparticle vaccines may also reach the lymph node by lymphatic drainage. In the lymph node, CD8 CTLs are produced by cross-presentation by lymph node DCs (Saxena and Bhardwaj 2017). Nanoparticle vaccines have a promising future in cancer treatment.

Another new type of adjuvant are self-polymerizing scaffolds. They are temperature sensitive biodegradable platforms that are made by the incorporation of TLR agonists and peptide antigens linked to a polymer scaffold. This adjuvant overcomes one of the biggest drawbacks with TLR adjuvants; the loss of potency through rapid dissolution at room temperature. The incorporation of TLR agonists and peptide antigens allows the molecule to remain water soluble at room temperature unlike TLR agonists. The scaffolds undergo temperature-dependent self-polymerization which makes immunogenic particles water soluble. These particles are drained to the lymph node where they activate DCs (Saxena and Bhardwaj 2017).

Albumin binding agonists are effective because of the abundance of albumin in the blood and lymph. Vaccines with albumin binding agonists have TAAs with lipid tails that have a high affinity for albumin. Once bound to albumin, the vaccine is taken to lymph nodes. Testing in mice has shown this vaccine type improves CD8 CTL activation by allowing vaccines to accumulate in lymph nodes (Saxena and Bhardwaj 2017).

Oncolytic viruses can also be used as vaccine adjuvants in oncolytic virus therapy, also known as virotherapy. This can be a useful vaccine adjuvant because oncoviruses are drawn to tumor cells. The biggest problem with virotherapy is that a virus specific immunity could develop to the oncolytic virus, weakening the antitumor response. A method to combat a virus specific immunity forming is administering sequential immunizations with different virus strains that express the same TAA (Saxena and Bhardwaj 2017).

Recent Research

The effects of the dopamine receptor DR3 on DC cross-presentation to T cells was examined by Figueroa *et al.* (2017). They used eight to twelve-week-old mice in all their experiments and generated DCs from the bone marrow of the experimental mice. One group of mice was wild type and the other was known as DR3 knockout mice, which had inhibited DR3 dopamine receptors.

They analyzed the role of D3R receptors expressed on DCs in antitumor immune responses by transferring wild type, or D3R-deficient, DCs into wild type recipient mice with tumors. In this experiment, the researchers saw a delay in tumor growth when mice received D3R-deficient DCs. This shows that the lack of D3R signaling in DCs leads to tumor immunity. In further experiments they used tumor-free animals. In these specific experiments, they saw D3R-deficient DCs promote stronger CTL responses than wild type DCs in tumor free mice by transferring DCs into tumor free mice and measuring their CTL production by removing splenocytes and using flow cytometry to determine the

number of CD8 T cells. This experiment revealed inhibition of D3R signaling leads to a better CTL response in both cancerous and healthy mice.

By co-culturing DCs from both groups of mice with antigen-specific CD4 T-cells, Figueroa *et al.* (2017) were able to determine the effect of D3R signaling in DCs on CD4 T cells. They found that CD4 T cell activation and function was similar with both groups of DCs. This experiment showed that D3R signaling does not have a significant role in activation of CD4 T cells.

Figueroa *et al.* (2017) analyzed CD8 T cell activation by testing DCs treated with the antagonist for D3R and using an enzyme-linked immunosorbent assay to test for activated CD8 T cells. The presence of the cytokine Interleukin-2 in the supernatant suggested activation of CD8 T cells because activated CD8 T cells secrete large amounts of this cytokine. The results showed an elevated level of CD8 T cell activation when D3R signaling was inhibited.

To determine how D3R signaling affected antigen cross-presentation, Figueroa and colleagues compared the amount of antigen cross-presentation in DCs that had inhibited D3R signals and those that did not have inhibited D3R signaling. The researchers used a monoclonal antibody that recognized the H2-Kb/OVA257-264 complex in peptide presentation of class I MHCs to measure the antigen cross-presentation in the wild type and D3R inhibited DCs that had been treated with D3R-selective antagonists. They found that the D3R inhibited DCs had a significantly higher degree of antigen cross-presentation than wild type DCs. From this result, Figueroa *et al.* (2017) were able to determine that the inhibition of D3R signaling in DCs enhances antigen cross-presentation into class I MHC and therefore improves CD8 T cell activation. This paper shows, dopamine decreases the antigen presentation by DCs to CD8 T cells. This knowledge could be used in cancer treatments with D3R inhibitors included in treatments.

Another new cancer treatment that is currently being investigated is the use of high hydrostatic pressure (HHP) treatment on cancer cells in conjunction with DC vaccines. HHP targets protein synthesis machinery and affects the structure and function of eukaryotic cells (Urbanova *et al.* 2017). DC vaccines consist of isolated DCs loaded with tumor antigen ex vivo. DC vaccines are administered as cellular vaccines (Timmeman and Levy 1999).

Urbanova and her colleagues (2017) investigated the effects of HHP on cancer cells and how it could affect dendritic cell-based cancer immunotherapy. This experiment examines the effects of HHP on cancer cells because of the known effects of HHP on eukaryotic cells. Urbanova *et al.* (2017) obtained and cultured prostate, ovarian, and lung human cancer cell lines for testing.

The cancer cells were treated with HHPs from 150-350 MPa for 10 or 15 minutes. The cells were then incubated and collected at different time points. After treatments, Urbanova *et al.* measured the tumor antigen protein (TAgP) content in human cancer cell lines. The membrane proteins were analyzed by western blotting directly after the cells thawed. The results demonstrated that the tissue origin of the cancer cell line and the magnitude of HHP applied determines whether HHP treatments were effective. They found that the HHP treatment did not have a significant effect on the TAgP content of prostate and ovarian cancer, but the lung cancer cell line tested was affected (figure 4). This suggests that the sensitivity of tumor cells to HHP treatments depends on the original tissue type the cancer cells were once a part of.

Using lung cancer cell line A549 expressing matrix influenza protein 1 (A549-MP1) as a model system, Urbanova and colleagues tested the effects of HHP on the production of CD8 T cells. Using flow cytometry, they observed the ability of DCs to phagocytose both lung cancer cells from the line H522 (figure 4) and from their model system mentioned above that had been treated with HHP. They observed more phagocytosis of both cell types at larger magnitude (200 or 250 MPa) HHP treatments

than with no treatment, but, saw no difference in the ability of DCs to phagocytose cells that had lower magnitude treatment (150 MPa) and control cells.

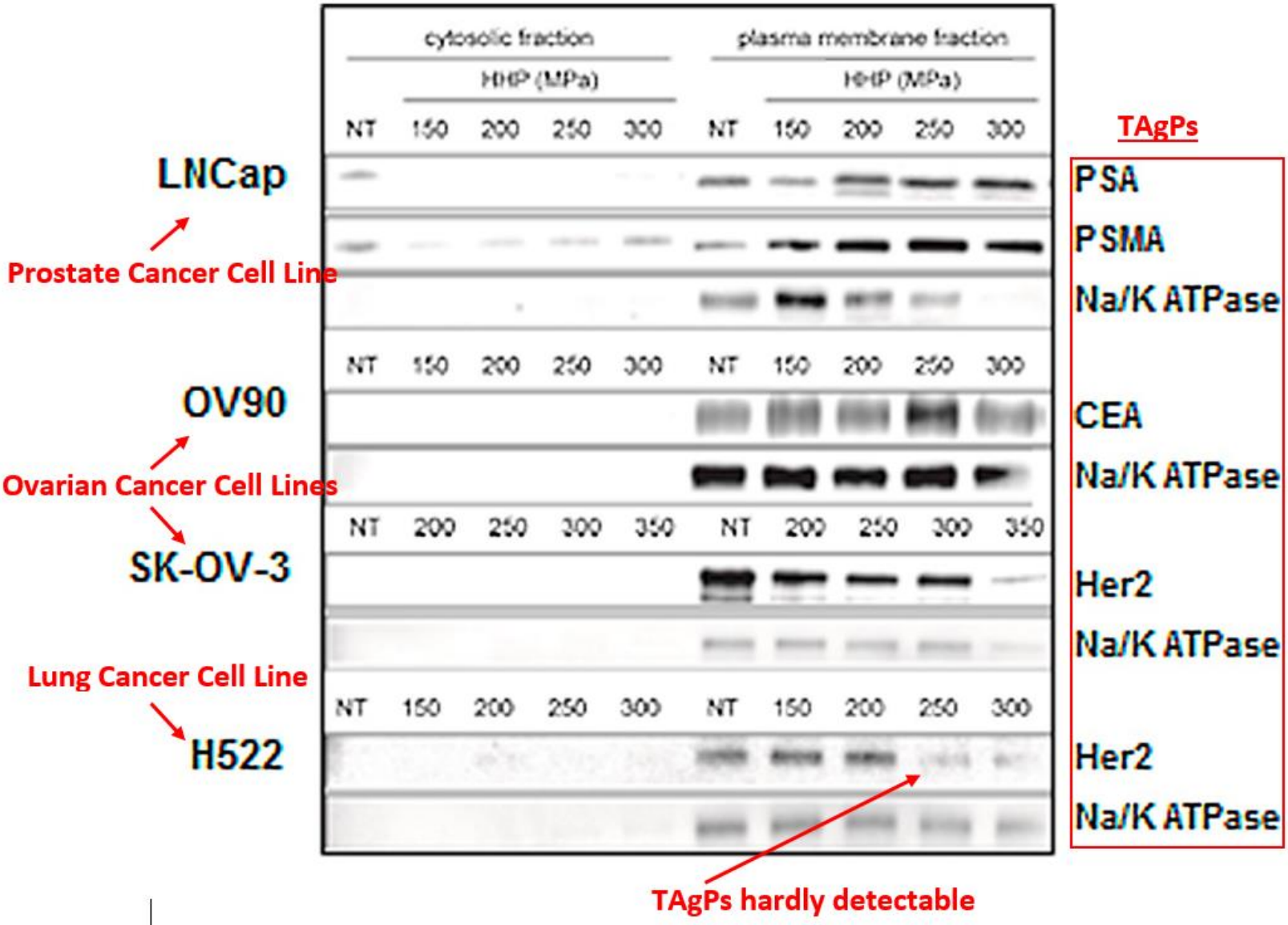


Figure 4. TAgP content in cells directly after thawing, shows that lungs cancer cells treated with 250 MPa and 300MPa have significantly lower amounts of TAgPs (Urbanova *et al.* 2017).

Again, using flow cytometry, the expression of CD8 T cells was measured. Urbanova *et al.* used an influenza matrix protein tetramer to detect CD8 T cells. They detected larger numbers of CD8 T cells in treatments with higher HHPs. However, the amounts of other T cells, such as CD4, CD25, and Foxp3 T cells were not affected by the HHP treatments.

Using clonogenic assays, Urbanova and colleagues were able to test the survival of cancer cells that had been treated with HHP DC vaccines. While they saw no survival of cancer cells that were treated with larger magnitude HHP treatments (200 and 250 MPa), cancer cells that had been treated with low magnitude HHP (150 MPa) vaccines had a significant level of survival despite these cultures having enhanced CD8+ T cell stimulation (figure 5).

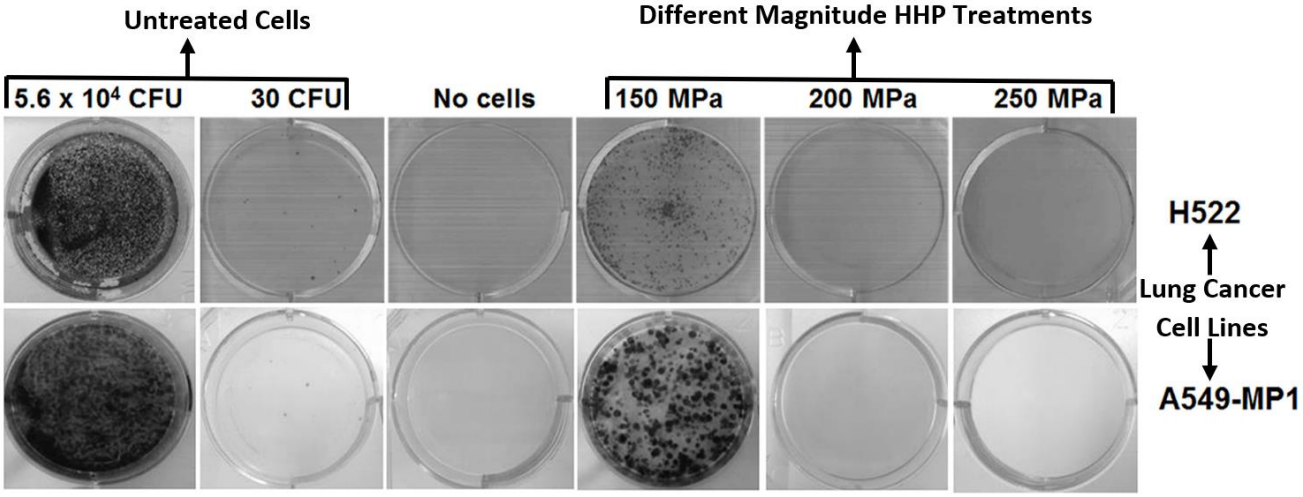


Figure 5. Clonogenic assays of lung cancer cell lines comparing HHP treated cells with untreated cells, cells treated with 200 MPa and 250 MPa show no growth (Urbanova *et al.* 2017).

Conclusion

In summary, these papers investigate the roles of DCs and T cells in the immune response to cancer. Specifically, they examine the mechanisms of dendritic cells in the tumor microenvironment. Figueroa *et al.* (2017) discovered DR3 dopamine signaling plays a vital role in the activation of CD8 T cells and the antigen cross-presentation from DCs to T cells. Urbanova and colleagues (2017) tested the effect of HHP treatments on DC based cancer vaccines. They found HHP treatment of cancer cells could be effective in aiding immunogenic antitumor responses to certain cancer cell lines. Although, there have been breakthroughs in cancer research and success in the research and development of new cancer treatments, cancer is still a large problem in today's society. Future studies should continue to address the different mechanisms involved in immune responses to cancer and investigate how these mechanisms can be manipulated to create novel treatments.

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