Overview in Tumor Immunology

Tumor Immunology- What is it? Lauren P.

The immune system plays a significant role in tumor prevention and control. Many decades of scientific research have revealed that the mammalian body utilizes effective mechanisms in the prevention of cancer cell development. These mechanisms occur at the DNA level and include nucleotide-excision repair, base-excision repair, homologous recombination, and end-joining (Hoeijmakers). However, when the DNA repair mechanisms are overcome, the immune system is an important player in cancer prevention. The immune response to tumor cells is largely due to expression of cell-surface indicators that do not exist on cells of normal function, and are recognized as antigenic species. Despite the prevalence of cancer, it is believed that tumor cells are generated in normal individuals throughout life, and are destroyed without notice by the normal immune effector mechanisms of the body. These mechanisms along with the greater understanding of the concept of immunosurveillance are a guide to better treat and prevent cancer. There are two major goals of tumor immunology: (1) to interpret the immunologic relationship between the host and the tumor, and (2) to take advantage of the normal immune response to better diagnose, prevent, and treat cancer patients. The foundation for achieving these goals is to better understand the initial immune response to tumor antigens, the immunologic factors influencing the incidence of cancer, the effector mechanisms for destroying tumor cells, and the cell-mediated response as well as being aware of the limitations of the immune system against tumors. In conclusion, the methods of immunodiagnosis and immunotherapy provide insight into the strategies being developed against cancer.

Tumor Antigens: Definition and Categories Sara B.

In the field of immunology, the interaction between cells of the immune system with tumor cells is called tumor immunology. Tumor immunology is concerned with two basic issues: (1) the above interaction and (2) the use of the immune response as a tool for **prevention, diagnosis, and therapy** against cancer (Coico and Sunshine, 2015, p. 312). Basically, cancer is an uncontrolled growth of cells, with a progression that leads to damage of critical tissues often leading to death. In 2017, the US is expected to have 1,688,780 case of cancer, resulting in 600,920 deaths. (Source: American Cancer Society).Tumor immunology is key to understand and to develop cancer treatments. The past twenty years of research show evidence that the immune system is responsible not only to protect, but also to control the progress of tumor cells. For instance, research shows how Ig A^+ B cells expressing PD-LI (programed death ligand 1) and interleukin 10 can promote the progress of cancer by limiting the activity of PD-1 expressing $CD8^+$ T cells (Shalapour *et al*, 2017). Acknowledging and relying in the guidance of our textbook by Richard Coico and Sunshine Geoffrey, 2015, in this part of our presentation, my

goal is to discuss one particular topic in tumor immunology: **tumor antigens, what are they and how do we categorize them**?

In short, tumor antigens are the molecules that will hopefully generate the immune response in the organism. Such response will occur as a reaction to the expression of some unusual cell surface component in malignant cells. Also known as tumor-specific transplantation antigens (TSTAS), tumor antigens initiate the immune response to tumor cells (Coico and Sunshine, 2015, p. 312). They are the initial players on how the immune system destroy tumor cells or how it fails to do so and cancer occur. Currently, we use several methods in molecular biology to identify these antigens, but I will not discuss them in my presentation because my goal is to briefly discuss **tumor antigens and the mechanism by which these antigens appear in the body (and by which they are categorized)**. Simplifying, I would say that as physicians and researchers two major classes of tumor antigens concern us: the ones that have common features and we may be able to target, and the unique ones that we are still looking for common features to target (the ones derived from carcinogens exposition, for instance). **Carcinogens** are molecule (natural or synthetic) or physical (radiation, for instance) agents that promote cancer formation by transforming cell DNA. We know that normal genes previously silent can be activated by carcinogens and we know that unique tumor antigens due to carcinogens are still products of mutated genes in hot spots locations. However, there is little to no cross-reactivity among carcinogen induced tumors (Coico and Sunshine, 2015, p. 313). Therefore, in this brief presentation we will focus on tumor antigens that have considerable immune cross-reactivity, the ones that we are able to target to improve cancer remission.

As any other antigen, in order to generate an immune response, tumor antigens must be immunogenic. In other words, they should be enough foreign-like, they must possess high molecular weight and enough chemical complexity. In addition, they must be degradable to be presented in the MHC complex of antigen presenting cells (APCs) (Coico and Sunshine, 2015, p. 312). **Why tumor antigens appear in the body and which are the features they have that allow their recognition as a threatening molecule?** From **oncogene theory,** we know that the genes susceptible to transformation by retroviruses are common to all vertebrate cells. These genes are highly conserved because they control key functions regulating cell growth. Often called proto-oncogenes or *c-onc* genes, these genes encode growth factors receptors, and signal transducers, for example. However, by which mechanism these genes become trouble makers? The short answer is mutation. When mutated via chromosomal translocation, point mutation and gene amplification, we say they are activated, and we call them oncogenes. Oncogene theory postulates that when proto-oncogenes are mutated they become overexpressed or express in the wrong tissues, showing abnormal growth mechanism of somatic cells. Such aberrant proliferation is seen at carcinoma in epithelial cells, sarcoma in muscles and connective tissues like fat and bones, leukemia in blood forming cells, like WBC, and lymphomas in lymphatic system, for instance (Coico and Sunshine, 2015, p. 315).

Tumor antigens appear in the body as a result of a mutation, a gene activation, which is not supposed to happen, or a clonal amplification of a mutated gene product (Coico and Sunshine, 2015, p. 312). As follow, we will briefly exemplify three main routes for tumor antigens formation. Via **(1)** Antigens that result from normal cellular gene production, in which something in the process became aberrant or out of place or time and they become amplified clones. Via **(2)** Antigens that are the product of mutant gene expression in somatic cells. Via **(3)** Antigens encoded by proto-oncogenes that are transformed into effective oncogenes due to viral transformation.

Examples of antigens resulting from **normal cellular gene production** (Via 1), also known as oncofetal antigens (Coico and Sunshine, 2015, p. 313):

- Cancer testes antigens **(CT**) these antigens are products derived from genes that should only be expressed in the male germline;
- Melanoma associated antigen (**MAGE**) this family of proteins should only be expressed in the testes adult tissue. However, several cancers like melanoma, carcinoma of the bladder, lung and liver show this abnormal expression;
- Carcinoembryonic antigen (**CEA**). It is seeing in the serum of patients with cancer of the colon, and in some cancers of stomach, breast, lung, pancreas. It is also seeing in non-neoplastic diseases (emphysema, ulcerative colitis, and pancreatitis) and in the sera of alcoholics and heavy smokers;
- a- fetoprotein (**AFP**) is a normal protein in the fetal and in the maternal serum, but it should be absent in other individuals, when it is not it is a tumor antigen. They are quite commonly observed in the BCR and TCR of malignant B cells and T cells, which produce amplified clones able to evade the immune surveillance of the body.

Examples of antigens resulting from **somatic mutations** (Coico and Sunshine, 2015, p. 314):

High amounts of tyrosine kinase from the *abl* gene amplified by a portion of the *bcr* gene becomes a tumor antigen. It is expressed in chronic myelogenous leukemia (CML) This tyrosine kinase amplification is the product of a gene reciprocal translocation of *bcr* gene on chromosome 22 and *abl* gene on chromosome 9, [t(9;22)], it results in shortened chromosome 22, known as Philadelphia chromosome. What does happen here? *bcr/abl* fusion gene encodes chimeric RNAs that translates into lots of tyrosine kinase, originally a product from the *abl* gene that here is amplified, and result in uncontrolled cell proliferation. Drug approved (2001): Bcr-Abl tyrosine kinase inhibitor (TKI).

Cyclin-dependent kinase-4 (**CDK-4**) that reduces the binding of its inhibitor, the tumor-suppressor protein known as p16INK-4 (p16). It is common in familial melanoma (pigment cell abnormal growth). What is happening here? CDK-4 becomes a tumor antigen when a mutation of the gene that encodes CDK-4 makes this kinase protein to have less affinity to its normal

inhibitor, the protein p16. Drug: Ribociclib. (a CDK4 and CDK6 inhibitor for estrogen receptor for $HER2^{+}$(human epidermal growth factor 2) used in breast and ovarian cancer).

Human epidermal growth factor receptor (HER) due to overexpression of the HER-2/neu-1 expression and common on certain breast and ovarian cancers.

Overexpression of mutant *p53* protein. This protein is immunogenic to B and T cells and results from mutations in highly conserved regions of the *p53* gene. These mutations make p53 protein unable to suppress cellular growth. Experiment in mice: transfer of cytotoxic T cells induced to react to normal p53, but without cause autoimmunity.

***ras* oncogene-encoded protein**. This mutated protein results from a glycine substitution in position 12 of the *ras* gene. It is a very common tumor antigen and present in prostate cancer, for instance.

Finally, there is large evidence implicating viruses in several human cancers. Some examples of antigens resulting from **oncogenes due to viruses** are (Coico and Sunshine, 2015, p. 315):

- DNA viruses: polyomavirus, SV40, and Shope papilloma virus;
- leukemogenic virus like the Rauscher leukemia virus, the human T-cell lymphotropic virus type 1(HTLV-1, which causes Adult T-cell leukemia), and
- Burkitt lymphoma, hepatocellular carcinoma, and nasopharyngeal carcinoma.

In contrast to the other categories of tumor antigens, virus antigens are expressed intracellularly. For example, for cytotoxic T lymphocytes (CTLs) to recognize tumor antigens, their epitopes must be processed and presented by class I MHC-associated peptides. In addition, the early stages of viral replication and cell transformation, an ***early region* gene** *E1A/E1B* and *E6/E7* is transcribed, for instance, during infection by adenovirus and human papilloma virus. Furthermore, virus induced tumors exhibit high cross-reactivity (Coico and Sunshine, 2015, p. 315). This means that a particular oncogenic virus induces the expression of the same antigens in a tumor no matter in which tissue. This characteristic is convenient and helpful in the identification and treatment of virus tumor antigen.

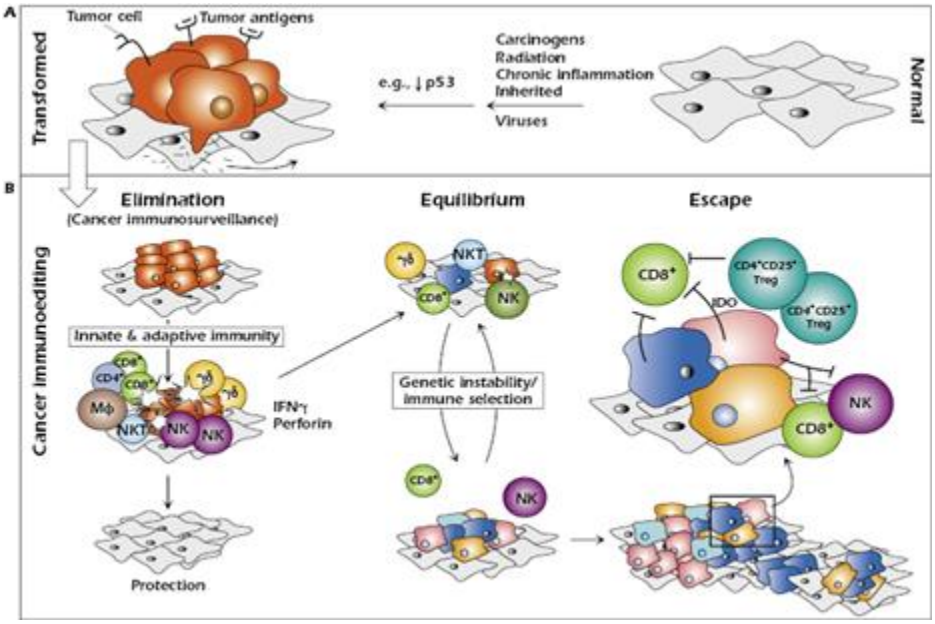
In conclusion, cancer is tissue damage due to uncontrolled cell growth due to problems in binary molecular switches (like tyrosine kinases and G proteins) that control intracellular signaling network in normal cell life, in particular during cell proliferation (Smithers and Overduin, 2016). Overall, there are two main types of tumor antigens: the ones activated by carcinogens and the ones activated by non-carcinogens. In non-carcinogenic, we can identify a common mechanism of cancer phenotype activation. Such mechanism is the overexpression and out of place expression of **normal cellular gene production of fetal and germ origin due to somatic mutations**, often, associated with **oncogenes due to viruses**.

How does immunology influence cancer? **Lauren P.**

While investigating the biological reason for the development of T-cell-mediated immunity in the 1950's, the term immunosurveillance was utilized to convey the concept of the body using its own immune system to act against the development and spread of cancer. The primary function of immunosurveillance was proposed to be specialized defense against altered self or neoplastic cells. The studies that centered around this concept revealed that higher incidences of cancer were observed in immunocompromised animals. However, it has also been observed that the most common forms of cancer are not seen with greater frequency in individuals that suffer from immunodeficiency diseases. Even with immunosurveillance and the natural development of these tumor-specific immune responses, cancer remains a common disease.

More recent studies have led to the hypothesis of immunoediting – a system enacted by the body's immune system upon the detection of cancer cells. The immunoediting hypothesis was termed as such after the finding that the immune system may also promote the growth of tumors that are able to escape recognition by the immune system, and therefore escape destruction. This hypothesis helps to "more broadly encompass the potential host-protective and tumor-sculpting functions of the immune system throughout tumor development" (Coico, 316). Immunoediting is considered a dynamic process consisting of three phases: (1) Elimination (2) Equilibrium and (3) Escape. Phase one, elimination, encompasses the classical concept of immunosurveillance where the cells and molecules of both the innate and adaptive immune system work in conjunction to potentially eradicate the developing tumor. These cells and molecules include macrophages, NK cells, NKT cells, $CD4^+$ T cells, $CD8^+$ T cells, and γδ cells.

Figure 20.1. Three phases of cancer immunoediting



If the elimination phase is not successful in the destruction of the tumor, the immunoediting system either moves to phase two, equilibrium, where the tumor cells are chronically maintained over a long period of time or undergo immunologic sculpting by immune "editors". It is this "editing" event that allows for new populations of tumor-cell variants to escape the control of the immune system and subsequently become clinically detectable in the third phase, escape. Phase two, equilibrium, is the period after tumor destruction has failed, and just before the escape phase where the tumor cells outweigh the balance of the immunological restraints of the equilibrium phase. The equilibrium phase includes NK cells, NKT cells, $CD8^+$ T cells, γδ cells as well as IFNγ and Perforin. The initiation of the cancer immunoediting process occurs early in tumor formation due to the distinct tumor-specific markers or tumor antigens present on the cell surface which generate "danger" signals alerting the immune system to begin phase one.

Both the innate and adaptive immune systems are essential for the effector mechanisms of tumor immunity. The ability of the immune system to act against tumor antigens depends on the type of tumor present and the context of antigen presentation. Studies have shown that the destruction of tumors *in vitro* by the immune effector mechanisms is more likely to be successful if the tumor cells exist as individual cells rather than a solid tumor. This is likely due to the simple fact that tumor cells are easier to attack when dispersed rather than when they are grouped together. Perhaps one of the largest roles in the immune response to cancer cells is played by the dendritic cells once they detect the "danger signals". This process is the same whether the dendritic cell encounters the signals due to cellular damage or the invasion of a foreign material or pathogen. Two events normally occur: the dendritic cells produce cytokines that lead to the differentiation of $CD4^+$ T_H0 cells into T_H1 cells allowing for further cell-mediated immune response or the activated dendritic cells lead to the polarization of T_H0 cells into T_H2 leading to an antibody response. Both events are theorized to be involved in the destruction of tumor cells.

Other effector mechanisms for responding to tumor cells include B cells, opsonization and phagocytosis, and the antibody-mediated loss of adhesive properties in tumor cells. The B cell response to tumor cells has been observed *in vitro* where, in the presence of complement, IgM and IgG antibodies destroy tumor cells. Studies *in vivo* have similar results where specific antitumor antibodies are involved in the destruction of certain cancer types and in reducing the metastases of others. Different studies that focused on the effects of the same antibodies with the help of complement factors against solid tumors did not show the same promising results. Two more findings based on *in vitro* studies were the opsonization and phagocytic destruction of tumor cells when in the presence of antitumor immune serum and complement, and antibodies specific for tumor-cell surfaces to interfere with the adhesive properties which are required for the cells to adhere to each other and surrounding tissue. The relevance of these two mechanisms *in vivo* is not currently known.

Cell-mediated response to tumor cells **Gabriela R.**

Tumors can be destroyed by T lymphocytes, antibody-dependent cell-mediated cytotoxicity (ADCC), natural killer [NK] cells, NK/T cells, cytokine-activated killer cells, and activated macrophages and neutrophils. Cytokines plays an important role in aiding the immune effector mechanisms in cancer immunity.

Virally induced tumors in vivo can be destroyed by tumor-specific cytotoxic T cells, with the aid of cytokines mediated by cytotoxic T lymphocytes (CTLs) such as IFN-γ and TNF-α. CD4+ helper T cells is involved in the induction, regulation, and maintenance of CTLs. Another destruction of tumor cells in vivo is by antibody-dependent cell-mediated cytotoxicity (ADCC). The process of ADCC in destroying tumor cells involves: the binding of tumor specific antibodies to the surface of the tumor cells, the interaction of granulocytes and macrophages which possess surface receptors for the Fc portion of the antibody attached to the tumor cell, and the destruction of the tumor cells by substances that are released from these cells that carry receptors for the Fc portion of the antibody (Coico). Natural Killer cells are involved in this process too, because they have Fc receptors.

Natural Killer cells (NK) are part of the lymphoid population primarily located in peripheral blood, lymph nodes, spleen, and bone marrow, in which they are able to lyse MHC class 1-negative tumor cells. Despite where the NK cells are located, chemokines can induce NK cells to migrate to inflammatory areas. Cytokine-activated tumor cells also known as lymphokine- activated killer [LAK] cells, are being used to destroy solid tumors by obtaining tumor-specific killer cells from patients. In addition, there's a newer strategy using T cells isolated from the tumor called tumor-infiltrating lymphocytes (TILs), which are then adoptively transferred to patients to destroy tumors. On the other hand, NK cells secrete TNF-α that induces hemorrhage and tumor necrosis. The mechanism for NK cells to recognize and kill tumor cells is unclear. In recent studies, it has been shown that NK/T cells are essential for tumor elimination in vivo (Coico).

In general, macrophages and neutrophils are not cytotoxic to tumor cells in vitro. However, macrophages and neutrophils can be activated by bacterial products in vitro to cause selective cytostasis or cytolysis of malignant cells. Moreover, when macrophages are activated by cytokines such as IFN-γ, produced by an activated population of T lymphocytes, they become highly cytotoxic to tumor cells. CD4+ T cells are tumor specific and release IFN-γ after activation by tumor antigens. In the meantime, other cytokines released by these antigen-activated T lymphocytes attract macrophages to the area of the antigen. IFN-γ also helps prevent the migration of macrophages away from the antigen. The mechanism of activation of macrophages by T cells specific for tumor antigens, leading to the destruction of tumor cells, starts off with an antigen activating the antigen-specific T cells which releases cytokines that attract and activate macrophages. These activated macrophages are cytotoxic to tumor cells, because they release lysosomal enzymes and TNF-α.

The destruction of tumor cells by activated macrophages occurs in vivo. It has been shown that resistance to a tumor can be abolished by a specific depletion of macrophages (Eubanks). In addition, increased resistance to tumors accompanies an increase in the number of activated macrophages. This such case has been seen at the site of regression of a tumor. However, the relationship between the tumor and the tumor-associated macrophages can be lethal or symbiotic, such as macrophages do killing tumor cells to macrophages and tumor cells producing reciprocal growth factors (Williams). Therefore, if there is a slight change in a symbiotic relationship between a macrophage and a tumor cell it will dramatically affect the reaction of the tumor.

The immune system is limited against tumors, and immunodiagnosis **Faiza Z.**

One of the immune system's common conflicts includes the daily battle against tumor cells. However, despite even the strongest efforts, there can still be limitations in the effectiveness in the immune response, and a tumor within a host can sometimes evade the immune system's attacks. In essence, the answer to why this occurs lies within one, or a combination of two factors – either linked to the tumor or the host. If they are successful, these factors serve as the key players to how a tumor can successfully avoid the immune system and continue to spread and become malignant.

If the issue stems to be tumor-related, it implies that either the tumor itself failed to serve as an adequate antigenic target (defective immunosensitivity), or the tumor simply failed to induce an immune response effective enough to combat it (defective immunogenicity). Within these two possibilities, the largest overall mechanism is the case where the tumor lacks a sufficient antigenic epitope. Defective immunosensitivity can also be expanded by the lack of MHC Class I molecules, efficient antigen processing by the tumor cell, antigenic modulation or masking of the tumor, and resistance of the tumor cell to the tumoricidal pathway. Alternatively, another cause of the tumor's escape may root from defective immunogenicity, an error in eliciting a proper immune response. In addition to lacking an epitope, other related mechanisms may include decreased MHC or antigen expression by the tumor, the lack of a co-stimulatory signal, the production of inhibitory substance (like cytokines) by the tumor, shedding of the tumor antigen and tolerance induction, as well as induction of T-cell signaling defects by the tumor burden. In addition, the stromal environment within the host serves as a key player in deciding whether or not a tumor cell gets destroyed in the immune system.

In the event that the root of the problem is unrelated to the tumor itself, host-related factors come into play where there is, rather, a failure in the host to respond to antigenic tumor cells. One of these mechanisms include immune suppression of deficiency of the host, and this can include an irregularity in apoptosis and signaling defects of T-cells due to carcinogen infections or simply aging. A list of some other mechanisms entail deficiency in APCs, a failure of host effectors to reach the tumor (due to a stromal barrier, for example), immunodominant

antigens, and T regulatory cells hindering tumor immunity. Due to the fact that tumors have such a large variance across the spectrum, there may also be nonspecific suppression mediated by these cells to reduce the immune response and effectiveness. For example, some tumors have the ability to synthesize various compounds like prostaglandins which contribute to a weaker immune response. However, there is still a lot of information, overall, which has many blank spaces and there is constant research being conducted to find the specific roles in these compounds and suppressive mechanisms. Ultimately, there are some rare instances when simply the size of the tumor growth is too large for the immune system to keep up with and there is a chance it can get overwhelmed.

A significant clinical step to combatting a tumor is the process of immunodiagnosis. For the most part, there are two fundamental goals that immunodiagnosis aims to achieve; detecting antigens specific to tumor cells or assessing the host's immune response to the tumor itself. The process is solidified based off of cross-reactivity and immunologic methods. Once a cell shows characteristics of being cancerous, it loses its antigenicity weakens, making immunodiagnosis more difficult. Therefore, newer studies have geared to utilizing monoclonal antibodies from mice in order to increase the specificity of immunodiagnosis. These antibodies serve multiple purposes including detecting antigens, detecting products associated with tumor cells, and efficacy in the localization of tumor cells. Today, some of the most commonly used and reliable immunodiagnostic procedures are performed for the following tumor antigens – myeloma proteins, alpha-fetaproteins, carcinoembryonic antigens, prostate-specific antigens, and cancer antigen-125.

Immunotherapy **Cindy G.**

The field of immunotherapy is quickly evolving. Several different techniques, all of which share the same goal, have been manufactured to treat the variety of cancers in existence. It was not until the current time and age where a large range of immunotherapeutic strategies have been manufactured. Included in the arsenal against cancer are monoclonal antibodies, bispecific antibodies, antibody drug conjugates, immunostimulatory monoclonal antibodies as well as other strategies used in cancer. Many of these strategies are currently being used or are in the process of clinical trials.

The monoclonal antibody technique can be approached one of two ways that include: engagement of Natural Killer (NK) cells through Fc receptors or by complement system activation. Monoclonal antibodies can be created to target many different cells in the body. Rituximab (anti-CD20) is the first man-made antibody approved by the U.S. FDA to treat B-cell lymphoma. Studies have demonstrated positive results with the use of Rituximab in combination with chemotherapy. Alternatively, xenogeneic chimeric antibodies or also known as mouse anti-human monoclonal antibodies, have been engineered using recombinant DNA to "humanize" their constant regions and are used as an antibody therapy. A number of treatments have quickly

been manufactured for the treatment of cancers. Many of these treatments are being evaluated or in the process of clinical trials. In addition, Bispecific antibody methods are being designed to bring immune effector cells in contact with tumor cells while stimulating the cytotoxic activity of these cells. This method is still under examination. Examples of this method include the use of antibodies to recognize the tumor antigens and IgG Fc receptors to activate NK cells. Also under investigation are antibody constructs containing Fabs that are specific to tumor antigens and CD3. Another approach involves the synthesis of recombinant fusion proteins that include anti-tumor antibodies and cytokines. These help by concentrating cytokine mediated immune effector responses at the tumor site. A fairly new approach involves the synthesis of recombinant fusion proteins that include antitumor antibodies and cytokines in the mix. Several approaches have been made to increase the response of tumor-specific CTLs. CTLs can be activated via tumor cells against tumor antigens that have been extracted as immunologic through the expression of co- stimulatory molecules like cytokines or CD80/CD86. A successful method that stimulates CTLs is the presentation of MHC class I tumor antigen peptides by DCs. A normal, highly efficient APC will express high levels of co-stimulating molecules at the cell's surface which in turn enhance the ability of presenting tumor antigens to effector T cells. Antibody- drug conjugates are molecules joined to a chemotherapy drug, radioactive particles, or toxins. The function of the antibodies acts on homing devices that take the molecules directly to the tumor. Many of these antibody-drug conjugates have been approved for use. Another approach involves immunostimulatory monoclonal antibodies. Specifically, targeted is anti-CTLA-4 that has been used with tumor vaccines to stimulate tumor response. CTLA-4 is considered a negative regulator of T cell response thus, potentially restricting anti- tumor immune responses. Monoclonal anti-CTLA-4 is an antibody that restricts CTLA -4 -mediated T cell suppression therefore enhancing the immune response against tumors. Similarly, an immunostimulant that recognizes programmed cell death receptor PD-1 interacts with ligands PD-L1 and PD-L2 causing the signal to become dampened. This inhibits the proliferation, decreases cytokine production, anergy, and/or apoptosis. Monoclonal antibodies have proven success in the treatment of tumors.

Other forms of nonspecific immunity have also been synthesized for the treatment of cancer. One form involve the stimulation of macrophages using BCG (bacille Calmette-Guerin) method has proven successful in some cases. Another fairly new methods use cytokines such as IFN-alpha, beta, and gamma; IL-1, IL-2, IL-3, IL-4, IL-5, IL-12, tumor necrosis factors, etc. This form unfortunately has had inconclusive results. Additionally, the use of chimeric antigen receptor therapy (CAR therapy) have had encouraging results and is making its way into clinical trials. Finally, the use of NKT cells as an ideal Anti- tumor immunotherapeutic factor is currently under examination. Studies done on lung cancer patients have proven success in prolonged survival time. Patients have experienced stable disease status or partial responses in head and neck cancers. This may well be the future of cancer treatments in an ever-evolving world of medicine.

Conclusion

Understanding the immune system interactions with tumor cells is not only the start of a field that has immense complexity, but also the beginning of a field with enormous potential. Tumor immunology is likely the future of cancer prevention, identification, and treatment. The human body is composed of a multilayered defense including genes, T effector cells, NKT cells, signaling molecules, etc. Particularly, in the immune system a variety of molecules interact with each other to keep the body in perfect homeostasis and away from harm. However, cancer develops when both uncontrolled cell proliferation and failure of the immunosurveillance system occur. This paper was an overview of tumor immunology discussing tumor antigens and their categories based on the mechanisms by which they may appear in the body. Also, it pointed out the oncogene theory, the dynamic process of immunoediting, and the cell-mediated response to tumor cells via tumor-specific cytotoxic T cells. Finally, it approached the evolving techniques of immunodiagnosis and immunotherapy. Such techniques like monoclonal antibody, engaging natural killer cell and nonspecific stimulation of macrophages using BCG are examples of new and revolutionary cancer treatments.

Works Cited

American Cancer Society. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html

Coico, R. and Sunshine, G. “Chapter 20: Tumor Immunology” In: *Immunology: A short course*, seventh ed., John Wiley & Sons Ltd., 2015, p. 312-315.

Coico, Richard, and Geoffrey Sunshine. “Chapter 20 Tumor Immunology / Immunologic Factors Influencing the Incidence of Cancer.” *Immunology: A short course*, seventh ed., John Wiley & Sons Ltd, 2015, p. 316.

Coico, Richard, and Geoffrey Sunshine. *Immunology: a short course*. seventh ed., John Wiley & Sons Ltd, 2015. Figure 20.1: Three phases of cancer immunoediting. Pg. 317.

Coico, Richard, and Geoffrey Sunshine. “Chapter 20 Tumor Immunology.” *Immunology: A short course*, seventh ed., John Wiley & Sons Ltd, 2015, pg. 318-319.

Hoeijmakers, J. H. J. (2001). Genome maintenance mechanisms for preventing cancer. *Nature, 411*(6835), 366-74. doi:http://dx.doi.org.ezproxy.lib.uh.edu/10.1038/35077232

Eubank TD, Roberts RD, Khan M, et al. GM-CSF Inhibits breast cancer growth and metastasis by invoking an anti-angiogenic program in tumor-educated macrophages. *Cancer research*. 2009;69(5):2133-2140. doi:10.1158/0008-5472.CAN-08-1405.

Shin-ichiro Fujii, Kanako Shimizu, Yoshitaka Okamoto, Naoki Kunii, Toshinori Nakayama, Shinichiro Motohashi, Masaru Taniguchi. “NKT cells as an Ideal Anti- Tumor Immunotherapeutic” Front Immunol. 2013; 4: 409. doi:10.3389/fimmu.2013.00409

Shalapour, Shabnam., Lin, Xue-Jia., Bastian, Ingmar N., Brain, John., Burt, Alastair D., Aksenov, Alexander A.,Vrbanac, Alison F., Li, Weihua., Perkins, Andres., Matsutani, Takaji., Zhong, Zhenyu., Dhar, Debanjan., Navas-Molina, Jose A., Xu, Jun., Loomba, Rohit., Downes, Michael., Yu, Ruth T., Evans, Ronald M., Dorrestein, Pieter C., Knight, Rob., Benner, Christopher., Anstee, Quentin M., Karin, Michael. Inflammation-induced IgA+ cells dismantle anti-liver cancer immunity. Nature, September, 2017. doi:10.1038/nature 24302

Smithers, C. C. and Overduin, M., Structural Mechanisms and Drug Discovery Prospects of Rho GTPases. Cells 2016, 5(2), 26; doi:10.3390/cells5020026.

Williams CB, Yeh ES, Soloff AC. Tumor-associated macrophages: unwitting accomplices in breast cancer malignancy.*NPJ Breast Cancer*. 2016;2:15025-. doi:10.1038/npjbcancer.2015.25.