



A Review on Immunity Against Tumor Cells

***Corresponding Author(s): Dr. Wengelu Welamo**

Department of Veterinary Medicine, Wolaita Sodo University, Ethiopia.

Email: wengewel293@gmail.com

Abstract

The immune response is a complex group of defense responses produced in both humans and advanced vertebrates that are involved in the elimination of abnormal somatic cells that develop into cancer. It occurs through the development of immunological memory through extensive effector functions to target and destroy pathogens, or through adaptive immune responses for subsequent defense mechanisms. This multifaceted mechanism consists of three main stages: elimination, equilibrium, and escape, each of which contributes to cancer elimination, quiescence, and progression. The purpose of this article is to review tumor immunotherapy. For this purpose, there are two forms of immune response. It is congenital, non-specific, fast-acting, first responder, and adaptable, characterized by specificity for target antigens, and acquires an immunological memory form. The former minimizes cancer-mediated inflammation, provokes an adaptive immune response, and attacks cancer through more specific immune mechanisms that can target antigens. The central doctrine behind the concept of cancer immunity is formation of neo antigens produced as a result of tumorigenesis/carcinogenesis that is phagocytosed by antigen-presenting cells (APCs) or pinocytosed by dendritic cells for antigen processing. Tumor growth can be controlled by antigen-specific or non-tumor-specific reactions. Tumor-specific immunity is predominantly mediated by both T cells and B cells, and non-specific tumor destruction is mediated by the innate immune system, independent of T cells, and is evoked by activating compounds that target pattern recognition receptors such as Toll-like receptors and Nod-like receptors. In summary, the immune system plays an important role in triggering an antitumor response and is changing rapidly, creating increasing excitement in human and veterinary medicine.

Received: Jun 10, 2022

Accepted: Jul 13, 2022

Published Online: Jul 15, 2022

Journal: Journal of Veterinary Medicine and Animal Sciences

Publisher: MedDocs Publishers LLC

Online edition: <http://meddocsonline.org/>

Copyright: © Welamo W (2022). *This Article is distributed under the terms of Creative Commons Attribution 4.0 International License*

Keywords: Adaptive Immunity; Cellular Immunity; Humoral Immunity; Immunotherapy; Tumor; Innate Immunity.

Abbreviations: ADCC: Antibody Dependent Complement Cytotoxicity; APC: Antigen Presenting Cells; CDC: Complement Dependent Cytotoxicity; CTL: Cytotoxic T Lymphocyte; CTLA: Cytotoxic T Lymphocyte-Associated Antigen; DAMPs: Danger Associated Molecular Patterns; HIF-1 α : Hypoxia Inducible Factor-1alpha; LAK: Lymphokine Activated Killer Cells; MDSC: Myeloid Derived Suppressor Cells; MHC: Major Histocompatibility Complex; MT: Liposomal Muramyl Tripeptide; NF κ B: Nuclear Factor Kappa B; NLR: Nod-like receptors; PAMPs: Pathogen Associated Molecular Patterns; ROS: Reactive Oxygen Species; TCR: T Cell Receptors; TLR: Toll-Like Receptors; TNF: Tumor Necrosis Factor; TRAIL: TNF related Apoptosis Inducing Ligand.



Introduction

Cancer cells are self-cells that have undergone changes or have bypassed normal growth-control mechanisms [42]. They are regular bodily cells that have been changed in such a way that they can continue to divide despite typical signals of constraint. As a result, cancer cells develop tumors, which penetrate and colonize tissues, eventually impairing organ function and resulting in death [65]. Cancer is a major public health issue that affects people all over the world and is one of the leading causes of morbidity and mortality [9]. Tumors grow when clones of altered cells proliferate and spread uncontrollably [13].

Immune responses are a sophisticated set of defense reactions produced by the immune system in humans and other advanced vertebrates that aid in the prevention of disease and infections. These immune responses may also aid in the elimination of cancer-causing aberrant cells in the body. The connection between the immune system and cancer has been well recognized for over a century, and Rudolph Virchow was the first to point it out over 150 years ago [36].

The underlying basis of this cancer-immunity relationship involves three basic principles about how the immune system works to protect and defend an individual: It detects antigens that are not from pathogens or infected/malignant cells; it includes effector functions to specifically target and destroy pathogens or infected/malignant cells while protecting the host; and it develops immunological memory through adaptive immune responses for further defense mechanisms following injury or host attack [39].

Through this process, the immune system has acquired pattern-generating features known as immune editing, which provides a balance between immune surveillance and cancer progression in the field of oncology [54]. This multifaceted mechanism involves three main phases: clearance, balance, and exit, which contribute to clearance, dormancy and cancer progression, respectively [72]. Interestingly, cancer's ability to evade or escape this immune response is now recognized as one of the most prominent features of cancer, providing the basis for treatments in immunotherapy. Although the early use of immunotherapy to treat cancer dates back to the early 19th century, this points to the work of William B. Coley and colleagues [3,36].

It is the responsibility of veterinarians to notice the growth patterns of tumor cells and their control by the immune system in the animals they care for. As the cancer hide itself, it can be left unnoticed in farm animals because they are thought to be disease-free and it remains serious due to its proliferative problem. Therefore, this review aims to evaluate tumor (cancerous) cells and their immunity against them, and to elucidate how immunity controls these out-of-control body cells.

Literature review

Tumor cells

Cancer cells are normal body cells that have become abnormal and continue to divide uncontrollably, despite normal signals telling them to stop. As a result, Cancer cells form groups of cells [65], called tumors, that invade and colonize tissues, eventually leading to organ dysfunction and death. Tumors are caused by the uncontrolled growth and spread of clones of transformed cells [13]. Cancer cells are mutated self-cells that have evaded the usual growth-control mechanisms [42].

Cancers that remain limited to their origin site are referred to as "primary cancer," but cancers that spread to other parts of the body are referred to as "secondary cancer or metastatic cancer." Certain altered cells are able to separate themselves from the main cancer development (neoplasm) and spread through other areas via lymphatic flow or blood circulation, which is how metastasis develops [26]. While metastatic malignancies retain the altered cells from the main tumour, they develop specific characteristics throughout time that assist differentiate them from the parent malignancy [49].

It's vital to remember that the terms "cancer" and "tumor" are not interchangeable. Tumors are clumps of aberrant cell growth (neoplasms) that can be benign or cancerous (injurious). These benign tumors stay isolated at the place of origin, whereas malignant tumors spread to other organs and are referred to as cancerous [26].

The onset of cancer

Cancer is caused by a variety of spontaneous and induced genetic mutations, including changes in glycosylation patterns, chromosomal gain or loss, and translocation [78]. DNA methylation and other epigenetic changes play a role in cancer etiology [79]. Hyper methylation, for example, is a known strategy for silencing tumor suppressor genes [25]. DNA hypomethylation of mobile DNAs, on the other hand, triggers gene activation and has been reported in a variety of malignancies [25]. These epigenetic alterations can affect a wide spectrum of tissues and organs, leading to cancers including prostate cancer and breast cancer [51].

Macrophages are thought to aid cancer cell proliferation by attracting oxygen-depleted tumor cells (hypoxic) and promoting chronic inflammation. The gene-switch nuclear factor-kappa B is activated by inflammatory chemicals generated by macrophages, such as tumor necrosis factor (TNF) [88]. NF B then reaches a tumor cell's nucleus and activates the synthesis of proteins that prevent apoptosis and promote cell proliferation and inflammation [90].

Not all cancer cells in circulation survive, but those that do can attach to the endothelial cell lining of capillary venules or blood arteries and travel to secondary tissues or organs via complex signaling pathways [62]. Cancers' hypoxic environment causes the development of proteins like hypoxia inducible factor-1alpha (HIF-1), which can control the expression of angiogenic growth factors like vascular endothelial growth factor (VEGF) [33].

Though a range of other proteins, such as cytokines, interleukins, and other growth factors, also have a role in cancer proliferation through angiogenesis [61]. Cancer or tumors can arise from a variety of tissues, including epithelium, mesenchyme (connective tissue/bones), or glands, and are classified as carcinoma, sarcoma, or adenocarcinoma, depending on the site of origin [9]. Lymphomas are cancers that begin in the lymphatic system and impact the lymphoid organs, whereas myeloma and leukemia are tumors that develop in the bone marrow and influence the formation of plasma cells in myeloma and erythrocytes and leukocytes in leukemia, respectively [34].

Immune System

The immune system is made up of a variety of soluble bioactive molecules, cytokines, proteins, and cells that work together to build a complex web of biochemical processes that recognize

and protect against “non-self” proteins or antigens [39]. The immune system consists of two types of immune responses: innate and adaptive, which provide protection and preserve the host’s normal state of homeostasis [39].

Innate Immunity and Cancer: Several components of innate immunity are engaged during cancer pathogenesis in order to reduce cancer-related inflammation (Dunn, 2006). This process also triggers adaptive immune responses, which allow more specialized immune systems to target the tumour [91]. Changes in the makeup of cancer cells’ cell surface proteins correspond with changes in their pathogenesis, resulting in the expression of tumor related antigens that can be identified by complement proteins, predisposing cancer cells to complement-mediated death (Pio *et al.*, 2014).

Innate immunity recognizes unique danger or pathogen associated molecular patterns (DAMPs or PAMPs) and uses receptors like TLRs and others to discriminate between self and non-self cells [39]. TLR7, for example, is an intracellular receptor that can recognize single stranded RNA but also suppresses Treg production, which is beneficial in the tumor setting [50]. Modified cell surface indicators and patterns on the surface of cancer cells occur from genetic and epigenetic change. MHC class I is one such cell surface marker whose expression is changed or diminished in cancer cells (Waldhauer, 2008). This abnormal or decreased MHC class I expression activates NK cells through activating receptors on the NK cell surface, such as NKG2D, which bind to surface glycol proteins called MICA/B that may be present on tumors (Steinle, 2008).

TNF-dependent release of cytoplasmic granules (perforin and granzymes) that form pores in cell membranes; antibody-dependent complement cytotoxicity due to the presence of antibody receptor (CD16) on NK cell surface; and the release of cytokines such as IFN-, which mediates activation and maturation of antigen-presenting cells such as dendritic cells, are all examples of NK-induced programmed cell death (apoptosis) (Waldhauer and Steinle, 2008). Phospholysosomes, found in neutrophils, include enzymes such as NADPH oxidase, which oxidizes superoxide radicals and other reactive oxygen species (ROS). ROS have been shown to not only promote cancer through genetic alterations caused by DNA damage, but also to induce cytotoxicity by disrupting the cell membrane on tumors [1].

In addition, different cell types act as evolutionary linkers between innate and adaptive immunity. Dendritic cells, $\gamma\delta$ T cells, macrophages, and NK T cells are examples of these cells. Dendritic cells and macrophages, for example, which serve as phagocytes in innate immune responses, can also serve as antigen-presenting cells in adaptive immunological responses [40]. NKT cells contribute to immune responses against tumor cells by secreting IFN, which activates the effector capabilities of cells like NK cells and CD8+ T cells, allowing them to cause tumor destruction via granzymes or perforin [53].

Similar to NK and CD8+ T cells, the $\gamma\delta$ T cells express NKG2D which interacts with MICA/B on tumor cells and promotes secretion of perforin proteins and subsequent tumor lysis (Gogoi and Chiplunkar, 2013). Other mechanisms implemented by the $\gamma\delta$ T cells for regulating cancer progression involve secretion of IFN- γ that can activate NK or CD8+ T cells for tumor lysis, recognition of tumor-associated antigens by CD16 (Fc receptor) to mediate antibody-dependent complement cytotoxicity, and the ability of $\gamma\delta$ T cell receptors to bind to self-antigens such as heat shock proteins that are upregulated in the cancer microenvironment [1].

Similarly, $\gamma\delta$ T cells, like NK and CD8 T cells, express NKG2D, which binds to MICA/B on tumor cells and increases perforin protein release and tumor lysis (Gogoi and Chiplunkar, 2013). T cells also regulate cancer progression through the secretion of IFN- γ , which can activate NK or CD8 T cells for tumor lysis, recognition of tumor-associated antigens by CD16 (Fc receptor) to mediate antibody-dependent complement cytotoxicity and the ability of $\gamma\delta$ T-cell receptors to bind to autologous antigens, such as heat shock proteins, are well regulated in the microenvironment [1].

Adaptive immunity and cancer

By utilizing the effect or functions of antibodies, T cells, B cells, and antigen-presenting cells, this type of immune response is capable of targeting antigens unique to cancer cells [73]. MHC class II molecules present foreign tumor antigen peptides, whereas MHC class I molecules present endogenous cancer antigen peptides [73]. MHC class II on APC activates CD4+ T cells, priming them for subsequent antigenic peptide/MHC class II complex exposures, resulting in the formation of memory T cells [98].

Thymus independent (TI) processes, which involve antigens with highly repetitive motifs, can activate B cells [10]. Antibodies that can bind to the tumor-derived antigen are produced once TI B cells are activated. This might cause tumor cell lysis via antibody-dependent complement cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), as well as attaching [28] to Fc receptors on NK cells [31]. The binding of antigen-specific T cell receptors with MHC class I/tumor antigen complexes activates CD8+ T cells, resulting in the induction of cytolytic CD8+ T cell-mediated destruction of cancer cells [91].

T cells contain a cell surface receptor molecule called programmed cell death protein 1 (PD-1) that can attach to its ligand, PD-L1, on APCs and mediates immunosuppression. The PD-1 expression has also been reported in multiple other immune cells such as B cells, NK cells, monocytes, dendritic cells, and Tregs [35]. Similar to CTLA4, the PD-L1 protein is expressed by a variety of cancer cells, suggesting that it may be a method by which cancer cells evade immunity [19]. Tregs can also suppress immune responses in an oncogenic setting (Nishikawa and Sakaguchi, 2010).

Cellular immunity

In a process known as cancer immune surveillance, the immune system may detect and eliminate emerging tumor cells, which serve as a key cancer defense [54]. The discovery of tumor-specific antigens has resulted in significant advancements in tumor immunology [63]. The majority of cancers are immunogenic, but the immunity they elicit is either insufficient to reject a fast growing tumor or the tumor causes the host immune system to become suppressed [106]. In the normal cellular fight against malignancies, several immunocyte populations are active. Macrophages, Natural Killer Cells, Cytotoxic cells, Chemokines, and Lymphokines are among them [74].

Cytotoxic T lymphocytes

These T lymphocytes are part of a subgroup of T lymphocytes that can kill infected or injured somatic and tumor cells. CTL responses are triggered when cytotoxic T cells identify antigen fragments [102]. These CTL responses are directed against the MHC-1 (MHC-I) molecule, which is linked to peptide antigens [15]. The pMHC-I complexes are expressed on infected cells and

are recognized by $\alpha\beta$ T cell receptors specifically [14]. T-cell like $\alpha\beta$ T-cell receptors (TCRs) play an important role in protective immunity because they may engage a wide range of foreign peptide-laden major histocompatibility complex (pMHC) landscapes (Gras *et al.*, 2011). Tumor related antigens with T cell epitopes have been shown to play an important role in tumor rejection. Tumor clearance is most likely the outcome of activating a robust and targeted immune response against tumor cells (Balashova, Lkhov, 2010).

Natural killer cells

Natural killer cells are a type of cytotoxic lymphocyte that makes up a large part of the innate immune system [6]. They eliminate foreign substances by releasing tiny proteins known as perforins and granzymes, which cause cells to undergo apoptosis and perish [41].

Macrophages

Macrophages are the cells that result from monocyte differentiation in tissues. They play a role in both innate and adaptive immune responses [16]. Macrophages kill tumor cells in an immunologically specific reaction that is followed by a nonspecific deadly reaction. For tumor cells, a variety of macrophage-released chemicals can have cytostatic and cytotoxic [96] effects. Various cytokines (INFs, TNF- α , IL-6, IL-1 (a/b), reactive oxygen or nitrogen intermediates, enzymes (e.g., arginase) metabolizing essential amino acids, prostanoid [77] metabolites (e.g. PGE2), and nucleotides (e.g. thymidine) mediate tumor cytostatic actions. The cytotoxic effect is mediated either by soluble factors (see above) or requires close contact between macrophages and the targeted tumor cells. TNF α plays an important role in macrophage-mediated cytotoxicity. TNF α -mediated killing is thought to occur through apoptosis induction and has been described in many cell types in vitro [76].

Dendritic cells

Dendritic cells are antigen-presenting cells (APCs) that play an important role in the regulation of the adaptive immune response [24]. Dendritic cells (DCs) are unique APCs and are referred to as "professional" APCs because the primary function of DCs is antigen presentation [21].

Lymphokines

Colony-stimulating factors (CSFs), Interferons (IFN -), Interleukins [87] (ILS 1-8, 10-13), and Tumor Necrosis Factor (TNF- α) [86] are examples of lymphokines produced by T-lymphocytes. In short-term experiments, lymphokines show a unique ability to destroy NK-resistant fresh human tumor cells [18]. At the population and clonal level, Lymphokine Activated Killer cells (LAK) appear to destroy autologous malignancies as well as TNP-modified self and allogeneic tumors with perfect cross reactivity. The systemic infusion of lymphokine activated killer (LAK) cells and recombinant interleukin-2 (RIL-2) has recently been found to be beneficial in lowering the amount of established lung and hepatic metastases from different mouse malignancies [47] and regulating the regression of metastatic cancer in humans [84].

Regulatory T cells

Regulatory T cells, also known as suppressor T cells, are necessary for immune self-tolerance and homeostasis [82]. Regulatory T cells limit the immune response to malignancy and prevent auto immune disorders by reducing self-reactive T

cells. Natural CD4+CD25+ T cells play a key role in autoimmune response suppression by inhibiting self-reactive T cells [23]. T cells are involved in the inhibition of viral, bacterial, and protozoal infection responses. CD4+CD25+ T cells were also discovered to inhibit protective antitumoral responses. Blocking Treg function using a neutralizing antibody against CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) resulted in an increase in protective immunological responses [94].

Myeloid derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a diverse group of cells that grow during cancer, inflammation, and infection and have a remarkable ability to dampen T-cell responses [56]. These cells are a special type of immune cell that modulates immunological responses in healthy people as well as in the setting of various disorders.

Humoral immunity

The non-cellular components of the blood, such as plasma and lymphatic fluid, are referred to as humoral. Immunologic responses mediated by antibodies are known as humoral immune responses [44]. The primary and secondary immune responses to antigen are referred to as humoral immunity. The host encounters an antigen for the first time during the initial immunological response. Before an effective immune response can be created, naive B cells must be activated and proliferated. Many pathogens may be too fast for this main response to guard against. Due to enhanced antibody binding affinities, the secondary antibody response, which occurs from the activation of a memory B cell, is faster and more efficient in preventing the progression of infection.

In neoplastic microenvironments, where they regulate tissue remodeling, pro-angiogenic (Shimoyama, 2011), and pro-survival pathways [67], humoral immune responses boost the recruitment and activation of innate immune cells [105]. The contact of the variable portions of an antibody with specific epitopes on cell-surface molecules triggers the humoral response. Oncoproteins, altered proteins like p53, are targets of tumor-specific humoral immune responses [64].

Conclusion

In general, the immune system is a natural defense system that plays an important role through cellular and humoral immunity in inducing anti-tumor responses. Cytotoxic T lymphocytes and natural killer cells induce tumor cell death by inducing a CTL response against tumor cells that are adhered to by MHC class I molecules mediated of antigen-presenting cells, while natural killer cells become killer cells activated by lymphokines and upregulate agents such as adhesion molecules, TRAIL, and TNF. TNF $\alpha\beta$ - is activated by macrophages and induces apoptosis. Dendritic cells help activate T cells, maintain immune tolerance and immune memory in B cells in tandem.

Although immune cells fight against tumor cells, some are involved in the formation of tumor cells, for example macrophages which are believed to help cancer cells to proliferate, by being attracted to oxygen-starved tumor cells and promoting chronic inflammation. Epigenetic alterations such as DNA methylation also play a role in carcinogenesis. Many proteins such as cytokines, interleukins, and other growth factors also contribute to angiogenesis for carcinogenesis. Therefore, further studies are needed to obtain immune cells that eliminate only tumor cells and improve them further.

References

1. Gregory AD, Houghton AM. Tumor-associated neutrophils: new targets for cancer therapy. *Cancer Res.* 2011; 71: 2411-6.
2. Sharpe AH. Mechanisms of costimulation. *Immunol Rev.* 2009; 229: 5-11.
3. Hoos A, Britten CM. The immune-oncology framework enabling a new era of cancer therapy a new era of cancer therapy. *Onco-Immunol.* 2012; 1: 334-9.
4. Aldrich JF, Lowe DB, Shearer MH, Winn RE, Jumper CA, Kennedy RC. Vaccines and immunotherapeutics for the treatment of malignant disease. *Clin Dev Immunol.* 2010; 2010: 697158.
5. Ammer AG, Kelley LC, Hayes KE, Evans JV, Lopez-Skinner LA, Martin KH, et al. Saracatinib impairs head and neck squamous cell carcinoma invasion by disrupting in vadopodia function. *J Cancer Sci Ther.* 2009; 01: 052-61.
6. Arjanova OV, Prihoda ND, Yurchenko LV, Sokolenko NI, Vihrova LA, et al. Impact of adjunct immunotherapy with multi-herbal supplement Dzherelo (Immunoxel) on treatment outcomes in end-stage TB/HIV patients. *J Antivir Antiretrovir.* 2009; 1: 86-8.
7. Bonta IL, Ben-Efraim S. Involvement of inflammatory mediators in macrophage antitumor activity. *J Leukoc Biol.* 1993; 54: 613-26.
8. Bottino C, Moretta L, Pende D, Vitale M, Moretta A. Learning how to discriminate between friends and enemies, a lesson from natural killer cells. *Mol Immunol.* 2004; 41: 569-75.
9. Blanpain C. Tracing the cellular origin of cancer. *Nat Cell Biol.* 2013; 15: 126-34.
10. Janeway CAJ, Travers P, Walport M, et al. B-cell activation by armed helper T cells. In: *Immunobiology: the immunesystem in health and disease*, Garland science, New York, NY, USA. 5th ed; 2001.
11. Carson WE, Giri JG, Lindemann MJ, Linett ML, Ahdieh M, Paxton R, et al. Interleukin (IL) 15 is a novel cytokine that activates human natural killer cells via components of the IL-2 receptor. *J Exp Med.* 1994; 180: 1395-403.
12. Chiplunkar SV. Immune system and cancer. *Princess Takamatsu Symp.* 1988; 19: 1-340.
13. Correll Abbey BS, Al B. Prostate cancer chemoprevention: A current review. *J Ferreira AK, Meneguelo R, Neto SC, Chierice GO, Maria DA. Synthetic phosphoethanolamine induces apoptosis through caspase-3 pathway by decreasing expression of Bax/bad protein and changes cell cycle in melanoma. J Cancer Sci Ther.* 2011; 3: 53-9.
14. Craig SC, Michelle AD, Whitney AM, James McCluskey JR. Specificity on a knife-edge: the ab T cell receptor. *Curr Opin Struct Biol* 16: 787-795. *cycle, Immunity.* 2006; 39: 1-10.
15. Dattatreya A, Sai YRKM, Anand SY, Mehaboobi S. A brief review on immune mediated diseases. *J Clin Cell Immunol.* 2011; 1: 001.
16. Debta P, Debta FM, Chaudhary M, Wadhwan V. Evaluation of infiltration of immunological cells (tissue eosinophil and mast cell) in odontogenic cysts by using special stains. *J Clin Cell Immunol.* 2010; 1: 103.
17. Dizdaroglu M, Jaruga P. Oxidatively induced DNA damage and cancer. *J Mol Biomark Diagn.* 2011; 2: 2.
18. Dronca RS, Markovic SN, Holtan SGH, Porrata LF. Neuro-endocrine-immune crosstalk and implications for cancer therapy. *J Cel Sci Therapy.* 2011; 2.
19. Contardi E, Palmisano GL, Tazzari PL, Martelli AM, Falà F, Fabbi M et al. CTLA4 is constitutively expressed on tumor cells and can trigger apoptosis upon ligand interaction. *Int J Cancer.* 2005; 117: 538-50.
20. Ehrlich R, Efrati M, Gonen B, Shochat L, Witz IP. Natural cellular defense activities against tumors--cytostasis and NK activity. *Haematol Blood Transfus.* 1983; 28: 470-1.
21. Wieder E. Dendritic cells: A basic review. *international society for Cellular Therapy;* 2003.
22. Forde PM, Reiss KA, Zeidan AM, Brahmer JR. What lies within: novel strategies in immunotherapy for non-small cell lung cancer. *Oncologist.* 2013; 18: 1203-13.
23. God JM, Haque A. Immune evasion by B-cell lymphoma. *J Clin Cell Immunol.* 2011; 2. Gregory SM, West JA, Damania B. Cancer vaccination, will you have to pay the toll? *J Vaccines Vaccin.* 2011; 1: 1.
24. Gregory SM, West JA, Damania B. Cancer Vaccination, Will You Have To Pay The Toll? *J Vaccines Vaccin.* 2011; S1: 1.
25. Akhavan-Niaki H, Samadani AA. DNA methylation and cancer development: molecular mechanism. *Cell Biochem Biophys.* 2013; 67: 501-13.
26. Lodish H, Berk A, Zipursky SL, Matsudaira P, Baltimore D, Darnell J. Tumor cells and the onset of cancer. *Mol Cell Biol.* 4th ed. 2000.
27. Nishikawa H, Sakaguchi S. Regulatory T cells in tumor immunity. *Int J Cancer.* 2010; 127: 759-67.
28. Schroeder HW, Cavacini L. Structure and function of immunoglobulins. *J Allergy Clin Immunol.* 2010; 125: S41-52.
29. Trollope A, Booth BA. 383. To E.S. Dallas. 1951; 22: 227-227.
30. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010; 363: 711-23.
31. Sun JC, Lanier LL. Natural killer cells remember: an evolutionary bridge between innate and adaptive immunity? *Eur J Immunol.* 2009; 39: 2059-64.
32. Crespo J, Sun H, Welling TH, Tian Z, Zou W. T cell energy, exhaustion, senescence, and stemness in the tumor microenvironment. *Curr Opin Immunol.* 2013; 25: 214-21.
33. Rundhaug JE. Matrix metallo proteinases, angiogenesis, and cancer: commentary re: A.C. Lockhart et al., Reduction of wound angiogenesis in patients treated with BMS-275291, a broad spectrum matrix metalloproteinase inhibitor. *Clin Cancer Res.* 2003; 9: 551-4.
34. Femand JP, James JM, Herait P, Brouet JC. Association chronic lymphocytic leukemia and multiple myeloma: origin from a single clone. *Blood.* 1985; 66: 291-3.
35. Podojil JR, Miller SD. Molecular mechanisms of T cell receptor and costimulatory molecule ligation/blockade in auto immune disease therapy. *Immunol Rev.* 2009; 229: 337-55.
36. Adams JL, Smothers J, Srinivasan R, Hoos A. Big opportunities for small molecules in immuno-oncology. *Nat Rev Drug Discov.* 2015; 14: 603-22.
37. Janelsins MC, Mustian KM, Peppone LJ, Sprod LK, Shayne M, Mohile S, et al. Interventions to alleviate symptoms related to breast cancer treatments and areas of needed Research. *J Cancer Sci Ther.* 2011; S2.

38. Janeway CA, Travers P, Walport M, Mark JS. Immunobiology: the immune system in health and disease. 5th ed; 2001.
39. Murphy K, Travers P, Walport M. Principles of innate and adaptive immunity. In: Janeway's immunobiology. 7th ed. New York: Garland Science Taylor & Francis Group; 2008. 1-38.
40. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. *Nat Rev Cancer*. 2012; 12: 265-77.
41. Karmakar S, Choudhury SR, Banik NL, Ray SK. Activation of multiple molecular mechanisms for increasing apoptosis in human glioblastoma T98G xenograft. *J Cancer Sci Ther*. 2010; 2: 107-13.
42. Kurioka D, Takagi A, Yoneda M, Hirokawa Y, Shiraishi T. Multicellular Spheroid Culture Models: applications in prostate Cancer Research and Therapeutics. *J Cancer Sci Ther*. 2011; 03: 60-5.
43. Sehn LH. Introduction to a clinical review series on aggressive B-cell lymphoma. *Blood*. 2015; 125: 1-2.
44. Lechleider R, Pastan I. Advances in the development of anti-CD22 immunotoxins containing pseudomonas exotoxin for treatment of hematologic malignancies. *J Cancer Sci Ther*. 2011; 03: 50-2.
45. Li J, Wang T, Zhang X, Yang X. The contribution of next generation sequencing technologies to epigenome Research of stem cell and tumorigenesis. *Hum Genet Embryol*. 2011; 2: 1.
46. Lim R, Lappas M, Ahmed N, Borregaard N, Quinn MA, et al. Effect of silencing neutrophil gelatinase-associated lipocalin in ovarian cancer cells on epithelio-mesenchymal transition. *J Mol Biomark Diagn*. 2011; 2: 114.
47. Lowe K, Jeyarajah DR. Integration of surgery and radioembolization in treatment of hepatic tumors. *J Nucl Med Radiat Ther*. 2011; 01: 105.
48. M, Papon J, Mishellany F, Denoyer D, Labarre P, et al. Promising preclinical validation of targeted radionuclide therapy using a [¹³¹I] labelled Iodoquinoline derivative for an effective melanoma treatment. *J Canc Sci Ther*. 2009; 1: 1-7.
49. Artac M, Bozcuk H, Ozdogan M, Demiral AN, Sarper A, Samur M et al. Different clinical features of primary and secondary tumors in patients with multiple malignancies. *Tumori*. 2005; 91: 317-20.
50. Dominguez-Villar M, Gautron AS, de Marcken M, Keller MJ, Hafner DA. TLR7 induces anergy in human CD4⁺ T cells. *Nat Immunol*. 2015; 16: 118-28.
51. Ehrlich M. DNA methylation in cancer: too much, but also too little. *Oncogene*. 2002; 21: 5400-13.
52. Gobert M, Treilleux I, Bendriss-Vermare N, Bachelot T, Goddard-Leon S, Arfi V et al. Regulatory T cells recruited through CCL22/CCR4 are selectively activated in lymphoid infiltrates surrounding primary breast tumors and lead to an adverse clinical outcome. *Cancer Res*. 2009; 69: 2000-9.
53. Terabe M, Berzofsky JA. The role of NK T cells in tumor immunity. *Adv Cancer Res*. 2008; 101: 277-348.
54. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. *Annu Rev Immunol*. 2011; 29: 235-71.
55. Maleki LA, Baradaran B, Majidi J, Mohammadian M, Shahneh FZ. Future prospects of monoclonal antibodies as magic bullets in immunotherapy. *Hum Antibodies*. 2013; 22: 9-13.
56. Manjili MH. Therapeutic cancer vaccines. *J Clin Cell Immunol*. 2011; 2: e101.
57. Mann AP, Tanaka T. E-selectin: its role in cancer and potential as a biomarker. *Transl Med Suppl*. 2011; 1: 2.
58. Martin KW, Hans S, Markwin PV. Tumour immunology Encyclopedia of Life Sciences. Nature Publishing Group; 2001.
59. McCormack E, Adams KJ, Hassan NJ, Kotian A, Lissin NM, Sami M, et al. Bi-specific TCR-antiCD3 redirected T-cell targeting of NY-ESO-1- and LAGE-1-positive tumors. *Cancer Immunol Immunother*. 2013; 62: 773-85.
60. Miller MJ, Foy KC, Kaumaya PTP. Cancer immunotherapy: present status, future perspective, and a new paradigm of peptide immunotherapeutics. *Discov Med*. 2013; 15: 166-76.
61. Nishida N, Yano H, Nishida T, Kamura T, Kojiro M. Angiogenesis in cancer. *Vasc Health Risk Manag*. 2006; 2: 213-9.
62. Reymond N, BB. D' 'Agua, and A.J. Ridley, "Crossing the endothelial barrier during metastasis,". *Nat Rev Cancer*. 2013; 13: 858-70.
63. Nagorsen D, Scheibenbogen C, Marincola FM, Letsch A, Keilholz U. Natural T cell immunity against cancer. *Clin Cancer Res*. 2003; 9: 4296-303.
64. Nayak BK, Krishnegowda NK, Galindo C, Meltz ML, Swanson GP. Synergistic Effect Between curcumin (diferuloylmethane) and Radiation on clonogenic Cell Death Independent of p53 in Prostate Cancer Cells. *J Cancer Sci Ther*. 2010; 02: 171-81.
65. Nguyen KT. Targeted nanoparticles for cancer therapy: promises and challenges. *J Nanomedic Nanotechnol*. 2011; 02: 103e.
66. O'Connor CM, Wilson-Robles H. Developing T cell cancer immunotherapy in the dog with lymphoma. *ILAR J*. 2014; 55: 169-81.
67. Osada S, Imai H, Sasaki Y, Yoshida K. Cryoablation-induced anti-cancer immune reaction. *J Clinic Experiment Ophthalmol*. 2011; 02: 1-5.
68. Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. *Clin Cancer Res*. 2013; 19: 5300-9.
69. Sheridan JP, Marsters SA, Pitti RM, Gurney A, Skubatch M, Baldwin D, et al. Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. *Science*. 1997; 277: 818-21.
70. Perez-Gracia JL, Labiano S, Rodriguez-Ruiz ME, Sanmamed MF, Melero I. Orchestrating immune check-point blockade for cancer immunotherapy in combinations. *Curr Opin Immunol*. 2014; 27: 89-97.
71. Pol J, Bloy N, Obrist F, Eggermont A, Galon J, Hervé Fridman W et al. Trial Watch: DNA vaccines for cancer therapy. *Oncoimmunology*. 2014; 3: e28185.
72. Schreiber RD, Old LJ, Smyth MJ. Cancer immune editing: integrating immunity's roles in cancer suppression and promotion. *Science*. 2011; 331: 1565-70.
73. Warrington R, Watson W, Kim HL, Antonetti FR. An introduction to immunology and immunopathology. *Allergy Asthma Clin Immunol*. 2011; 7: article S1.
74. Razmkhah M, Jaberipour M, Ghaderi A. Chemokines and chemokine receptors expression in the adipose derived stem cells (ASCs), breast tissues and in peripheral blood of patients with breast cancer. *J Carcinogene Mutagene*. 2011; 2: 120.
75. Rannug A, Rannug U, Ramel C. A new mechanism for mutagens/carcinogens. A new mechanism for mutagens/carcinogens. *Mutation Research/Environmental Mutagenesis and Related Subjects*. 1984; 130: 188.

76. Robaye B, Mosselmans R, Fiers W, Dumont JE, Galand P. Tumor necrosis factor induces apoptosis (programmed cell death) in normal endothelial cells in vitro. *Am J Pathol.* 1991; 138: 447-53.
77. Rubenstein M, Hollowell CM, Guinan P. Enhanced Delivery of Chemotherapeutic Alkylating Agents into Prostate Cancer Cells Employing the Androgen Receptor as Delivery Vehicle. 2011; 01.
78. Pinho SS, Reis CA. Glycosylation in cancer: mechanisms and clinical implications. *Nat Rev Cancer.* 2015; 15: 540-55.
79. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. *Carcinogenesis.* 2010; 31: 27-36.
80. Saikh KU. Innate immunity and sepsis: MyD88 as a target for therapeutics. *J Clin Cell Immunol.* 2011; 2: e102.
81. Serfin J, Carragher J, Groman A, Dexter EU, Yendamuri S. Outcome Prediction Using Markers of Aerobic Glycolysis (the Warburg effect) Varies Between Tumor Regions in Stage I non-small Cell Lung Cancer. *J Mol Biomark Diagn.* 2011; 2: 116.
82. Sakaguchi S. Regulatory T cells. *Springer Semin Immunopathol.* 2006; 28: 1064.
83. Shimoyama S. BRAF mutations and their implications in molecular targeting therapies for gastrointestinal cancers. *J Pharmacogenom Pharmacoproteomics.* 2011; 02: e102.
84. Shimul S, Rajiv G. MTA1 Aids the AKT pathway by inhibiting expression of a key regulator, PTEN. *J Cancer Sci Ther.* 2010; 2: 114-9.
85. Shirole AB, Sylvester PW. Mechanisms mediating the synergistic anticancer effects of combined γ -tocotrienol and celecoxib treatment. *J Bioanal Biomed.* 2011; 3: 1-7.
86. Shrihari TG. Cancer stem cells – therapeutic boon! *J Cancer Sci Ther.* 2011; 3: 197-200.
87. Singh RK, Sudhakar A, Lokeshwar BL. Role of chemokines and chemokine receptors in prostate cancer development and progression. *J Cancer Sci Ther.* 2010; 2: 89-94.
88. Singh RK, Sudhakar A, Lokeshwar BL. From normal cells to malignancy: distinct role of pro-inflammatory factors and cellular redox mechanisms. *J Cancer Sci Ther.* 2011; 3: 70-5.
89. Sinnathamby G, Zerfass J, Hafner J, Block P, Nickens Z. EDDR1 is a potential immunotherapeutic antigen in ovarian, breast, and prostate cancer. *J Clin Cell Immunol.* 2011; 2: 106.
90. Skopec R. Mechanism linking aggression stress through inflammation to cancer. *J Cancer Sci Ther.* 2011; 03: 134-9.
91. Sliwkowski MX, Mellman I. Antibody therapeutics in cancer. *Science.* 2013; 341: 1192-8.
92. Son CH, Bae JH, Shin DY, Lee HR, Choi YJ, Jo WS, et al. CTLA-4 blockade enhances antitumor immunity of intratumoral injection of immature dendritic cells into irradiated tumor in a mouse colon cancer model. *J Immunother.* 2014; 37: 1-7.
93. Srivastava M, Eidelman O, Bubendorf L, Sauter G, Pollard HB, et al. Loss of ANXA7 expression is associated with poor patient survival in ovarian cancer. *J Mol Biomark Diagn.* 2011; 2: 113.
94. Beissert S, Schwarz A, Schwarz T. Regulatory T cells. *J Invest Dermatol.* 2006; 126: 15-24.
95. Stroncek DF, Berger C, Cheever MA, Childs RW, Dudley ME, Flynn P, et al. New directions in cellular therapy of cancer: a summary of the summit on cellular therapy for cancer. *J Transl Med.* 2012; 10: 48.
96. Su X, Xu C, Li Y, Gao X, Lou Y. Antitumor activity of polysaccharides and saponin extracted from sea cucumber. *J Clin Cell Immunol.* 2011; 2: 105.
97. Sun CZ, Lu CT, Zhao YZ, Guo P, Tian JL, et al. Characterization of the doxorubicin-pluronic F68 conjugate micelles and their effect on doxorubicin resistant; 2011.
98. Harris TJ, Drake CG. Primer on tumor immunology and cancer immunotherapy. *J Immunother Cancer.* 2013; 1: article12.
99. Thomas S, Waterman P, Chen S, Marinelli B, Seaman M, Rodig S, et al. Development of secreted protein and acidic and rich in cysteine (SPARC) targeted nanoparticles for the prognostic molecular imaging of metastatic prostate cancer. *J Nanomed Nanotechnol.* 2011; 2.
100. Tan TT, Coussens LM. Humoral immunity, inflammation and cancer. *Curr Opin Immunol.* 2007; 19: 209-16.
101. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. *Annu Rev Immunol.* 2011; 29: 235-71.
102. Williamson NA, Rossjohn J, Purcell AW. Tumors reveal their secrets to cytotoxic T cells. *Proc Natl Acad Sci U S A.* 2006; 103: 14649-50.
103. Wu YL, Liang J, Zhang W, Tanaka Y, Sugiyama H. Immunotherapies: the blockade of inhibitory signals. *Int J Biol Sci.* 2012; 8: 1420-30.
104. Minami Y, Kono T, Miyazaki T, Taniguchi T. The IL2 receptor complex: its structure, function, and target genes. *Annu Rev Immunol.* 1993; 11: 245-68.
105. Yadav B, Greish K. Selective inhibition of hemoxygenase-1 as a novel therapeutic target for anticancer treatment. *J Nanomed Nanotechnol.* 2011; 4: 5.
106. Yokoe H, Kasamatsu A, Ogawara K, Ishigami T, Sato Y, et al. Neoadjuvant chemotherapy with S-1 for patients with oral squamous cell carcinoma. *J Cancer Sci Ther.* 2010; 2: 132-5.
107. Zhang Y New Concepts of Germline Gene -reactivated Cancer. *New Concepts of Germline Gene –reactivated Cancer. Human Genet Embryol.* 2011; 01.
108. Zigler M, Shir A, Levitzki A. Targeted cancer immunotherapy. *Curr Opin Pharmacol.* 2013; 13: 504-10.