ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 08, pp.6429-6432, August, 2019

DOI: https://doi.org/10.24941/ijcr.36407.08.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

CANCER VACCINES: NOVEL STEP TOWARDS CANCER TREATMENT

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ARTICLE INFO

Article History:
Received 17th May, 2019
Received in revised form
25th June, 2019
Accepted 19th July, 2019
Published online 31st August, 2019

Key Words:
Cancer,
Cancer Vaccine,
Recombinant Vaccine,
Cancer therapy.

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ABSTRACT

Cancer in an multifactorial disease that occurs due to the uncontrolled cell division which invades surrounding tissue replacing native cells and ultimately resulting into the disease leading to death. Development of high throughout cancer vaccine is the need of the century in order to control increasing incidence of death among cancer patients. The aim of cancer vaccines is to stimulate the immune system of the individual, to be able to recognize and differentiate cancer cells as abnormal and destroy them specifically. Current research in field of molecular biology and immunology has resulted in the development of a range of recombinant vaccines viz., antigen, tumor cell, anti-idiotype antibody-based, dendritic cell-, DNA-, and viral- vector based- vaccines. Although success of cancer vaccine appears to be limited, still one such mile stone treatment for cancer is giving hope to the people in order to get cure. Cancer vaccines have been exclusively studied all through the past decades, and have made exceptional achievements in cancer treatment. Few cancer vaccines have been approved by the US Food and Drug Administration (FDA) Majorly, cancer vaccine research is in progress to develop universal as well as specific cancer vaccine. the present presentation briefly details about the recent developments in cancer therapy especially by empahising vaccine development against cancer.

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***Citation: Shivani Jani, Nimesh Rupala and Priya Mehta,* 2019.** "Cancer vaccines: novel step towards cancer treatment", *International Journal of Current Research*, 11, (08), 6429-6432.

INTRODUCTION

Cancer grow when normal cells can grow in a specific part of the body begin in out of control. There are many types of cancers; all types of cancer cells can grow, divide and multiply instead of dying and form new abnormal cells. Through blood circulation or lymph node, some type of cancer cells repeatedly travel to other parts of the body. where they begin to grow.(Sudhakar, 2009) Due to the environmental factors that mutate genes encoding critical cell- regulatory proteins and then caused cancer. The resultant abnormal cells that destroy surrounding normal tissue and spread to other organs resulting in circulated disease, (Menaria, Kitawat, Verma, & Menaria, 2013) However the significant increasing in recent years towards the development of new targeted therapies, cancer survive a largely unmet medical need and the leading cause of death in industrialized countries.(Menaria *et al.,* 2013). Worldwide in 2000, cancer caused 6.7 million deaths. The World Health Organization estimated that if unchecked, annual global cancer deaths could rise to 15 million by 2020.(Menaria *et al.,* 2013) Currently there are several techniques that are being used to treat cancer like Angiogenesis Blockers, Bone Marrow Transplants, Chemo Therapy, Cryosurgery, Gene Therapy, Laser Therapy, Photodynamic Therapy, Radio Therapy & Stem Cell Therapy (Menaria *et al.,* 2013).

Scientists are developing several experimental cancer vaccines that could lead to the destruction of cancer this century. The word cancer vaccine indicates to a vaccine that preventsan infections caused by cancer viruses, treats existing cancer or prevents the development of cancer in certain high risk individuals (Menaria *et al.,* 2013).Vaccines against infectious agents is one of the great successes of medicine which acts to prevent diseases. These vaccines, which are designed to generate humoral (antibody-based) immunity, have mostly been identified in an empirical manner (Banchereau and Palucka, 2017).

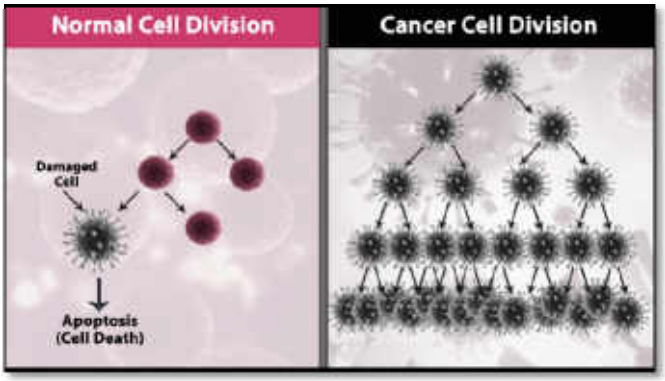
There are two main broad categories of cancer vaccines

Preventive (or prophylactic) vaccines: which are intended to prevent cancer from developing in healthy people.(Menaria *et al.,* 2013)

Treatment (or therapeutic) vaccines: which are intended to treat an existing cancer by strengthening the body's natural defenses against the cancer. There are two major types of this categorycancer vaccines:

Specific Cancer Vaccines – Treat specific type of cancers. Different vaccines are needed to treat different types of cancers.

Universal Cancer Vaccines –Fight cancer cells regardless of cancer type (Menaria *et al.,* 2013)



(Source: DrJockers.com)

Figure 1. Cell Division of Normal Cells and Cancerous Cells

Different types of cancer Vaccines

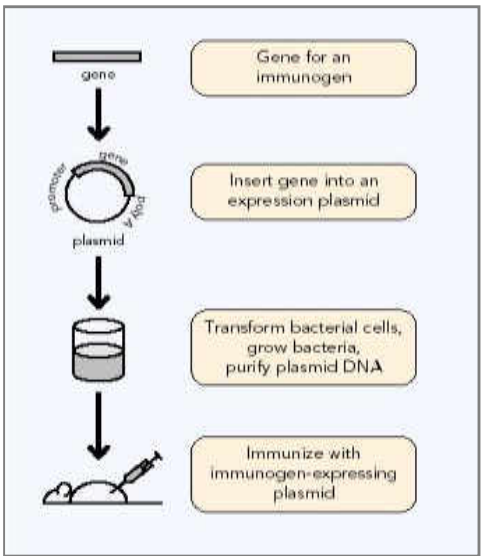
- Dendritic cell vaccines
- DNA vaccines
- Tumor cell vaccines
- Idiotype vaccines

Dendritic Cell Vaccines

Dendritic cells (DCs) are considered the most potent APC of the immune system, and are unique in their ability to stimulate naïve T cells. DCs are adapted to capture proteins, proteolytically digest them, and present the resulting peptides on their cell membranes bound to MHC antigens (Benjamin *et al.,* 1999). Several DC-based cancer vaccines have been developed to date including DC loaded with, tumor peptides or whole proteins (Li *et al.,* 2000), with tumor-derived mRNA or DNA (Van *et al.,* 2001), DC transduced with viral vectors such as retroviruses (Ardeshna *et al.,* 2000), lentiviruses (He *et al.,* 2005), adenoviruses (Di Nicola *et al.,* 2000), fowl pox (Kim *et al.,* 1998) and alphaviruses (Caley *et al.,* 1997) containing the tumor antigen or gene of interest, whole necrotic or apoptotic tumor cells (Chen *et al.,* 2001), tumor cell lysates (Ferlazzo *et al.,* 2000) and DC-fused with tumor cells (Gong *et al.,* 2000; Avigan *et al.,* 2012). Whole necrotic or apoptotic tumor cells, tumor cell lysates and DC-fused with tumor cells. Although the potential of DC-based vaccines to induce an antigen-specific response have been shown in many clinical trials and preclinical animal models (Schuler *et al.,* 2003), choosing the best DC population from several DC cell subsets with distinct properties and functions has been a challenge. Each subset of DC has a unique capability of activating Th1, Th2 or Th17 cells. Once a particular DC subset has been isolated or generated, it must undergo a maturation process to enhance its ability to activate T cells (Yamazaki *et al.,* 2006). Many animal studies have determined that the DCs/tumor fusion vaccine not only provided protection against challenge with tumor cells, but also degenerated established tumors, including melanoma, colorectal, breast, esophageal, pancreatic, hepatocellular ,lung, laryngeal, renal cell carcinoma, sarcoma, myeloma, mastocytoma , and neuroblastoma.(Menaria *et al.,* 2013)

DNA Vaccine

DNA vaccines are the new breakthrough in the field of immunization and are quite different from traditional vaccines. In DNA vaccines, the gene coding antigenic protein which is responsible for causing the disease, protein, that are identified and isolated from the pathogen and injected into a vector (plasmid) carrying the gene into the living system. The plasmid carrying the gene is inserted into the muscle cells and is adapted into antigenic protein that evokes the immune response normally produced by the pathogen. It is different from recombinant vaccine, where the gene coding for the antigenic protein is expressed in a prokaryotic system (Gurunathan *et al.,* 2000; Kennedy *et al.,* 2010; Donnelly *et al.,* 1997; Davis *et al.,* 1996; Hermanson *et al.,* 2004). DNA vaccine is introduced into a cell, such as a muscle cell, it makes its way into the nucleus of the cell and directs the cell's synthetic machinery to synthesize proteins encoded by the gene on the plasmid. The antigenic proteins are released outside the cell. (Saha *et al.,* 2011). There are a lots advantages of DNA vaccines. DNA vaccines stimulate both arms of the immune system providing stronger protection against pathogens. DNA vaccine can also provide immunity against many strains of a single pathogen in a single vaccine. The plasmid vector used to carry the gene of interest is highly enriched in CG sequences flanking the arm containing the gene coding for the antigenic protein. (Saha *et al.,* 2011). There are certain limitations of DNA vaccines such as that they cannot be used against certain microbes (e.g. pneumococcus) that uses outer capsular structures made of polysaccharides as DNA can only be used to target protein component of the pathogens. (Saha *et al.,* 2011)

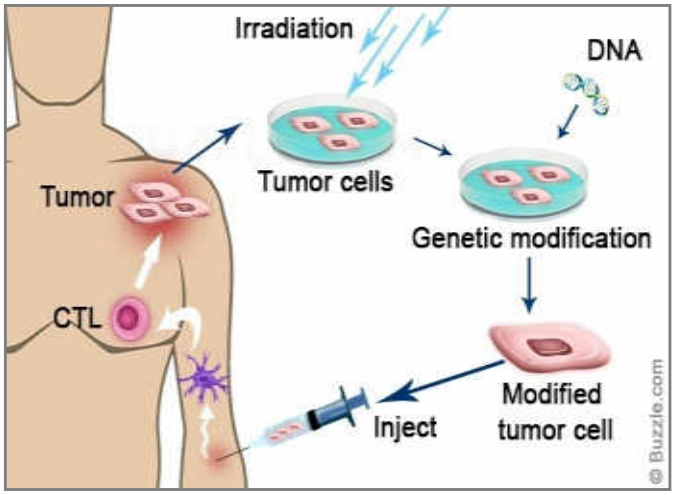


(Source: ENCKE. J. et al., 1999)

Figure 2. DNA Vaccines

Tumor Cell Vaccine

Autologous and allogeneic tumor cells were one of the first types of tumor vaccines to be used (Livingston *et al.,* 1983; Livingston *et al.,* 1982). Theoretically, the main advantage of tumor cell vaccines is that they have all the applicable tumor antigens needed by the immune system to mount an effective antitumor response. A second advantage is that tumor cell-based immunization allows the development of cancer vaccines without knowing the specific antigens. Mainly the advantages of tumor cell-based cancer vaccines must be equivalent against two major disadvantages: the potential for autoimmunity and the potential for increasing the anergic status of the T cells due to the lack of functional co-stimulatory molecules on tumor cells.(Vaccines, 2002).



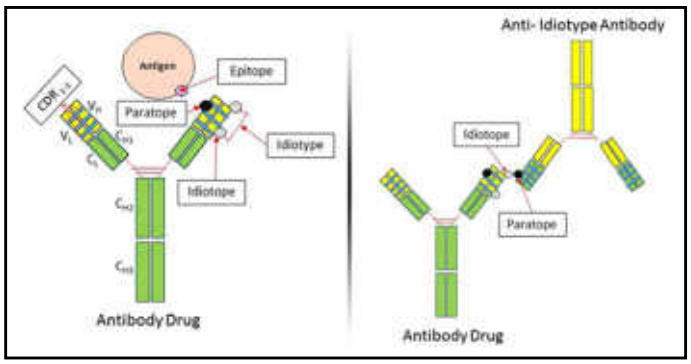
(Source: buzzle.com)

Figure 3. Tumor Cell Vaccines

Anti-Idiotype Vaccine

Immunoglobulin (Ig) molecules contain highly specific, unique peptide sequences in their variable regions at the antigen-combining sites in the complementary-deter- mining regions. The variable regions of heavy and light chains combine to form the unique antigen recognition site of the Ig protein. These variable regions contain determinants that themselves can be recognized as antigens, or idiotypes. Non-Hodgkin's lymphomas are usually clonal proliferations of B cells synthesizing a single type of antibody molecule with a unique variable region that can serve as tumor-specific antigen (Stevenson and Stevenson, 1975). And, therefore, can be targeted for cancer vaccination. Follicular lymphomas also are associated with a characteristic translocation that brings the bcl-2 gene on chromosome 18 under the transcriptional control of the Ig heavy-chain gene located in chromosome 14.

This translocation, t(14-18), has been used as a molecular 27 marker for minimal residual disease (Lee *et al.,* 1987). Although the long-term clinical relevance of molecular remission in follicular lymphoma remains to be ascertained (Gribben *et al.,* 1991; Lopez-Guillermo *et al.,* 1998), it is clear that idiotype vaccination either reduces the tumor burden beyond that already achieved by chemotherapy or leads to the redistribution of residual tumor cells to sites other than peripheral blood. These two trials provide strong evidence for an antitumor effect of lymphoma-specific vaccination. A multicenter, prospective, randomized trial is being conducted to further evaluate whether idiotype vaccination results in long-term clinical benefit. Although chemotherapy followed by idiotype vaccination with or without GM-CSF seems to be an effective regimen to immunize against lymphoma, several investigators are trying to improve this approach. One process under evaluation is the use of DCs pulsed with idiotype protein (Hsu *et al.,* 1996). Another approach to idiotype vaccination for non-Hodgkin's lymphoma is based on animal and human studies, which have shown that, in an allogeneic setting, immunity to certain antigens could be transferred from the marrow donor to the patient (Grosse-Wilde *et al.,* 1986; Lum *et al.,* 1986). The strategy entails the immunization of the immunologically competent and normal allogeneic donor with the idiotype vaccine derived from the recipient's tumor before harvesting the stem cells to be used in the transplant.



(Source: GeneScript.com)

Figure 4. Anti-Idiotype Vaccines

Limitations of Cancer Vaccines

Today, most cancer vaccines are targeted. The limitations of targeted vaccines are similar to the limitations of other targeted therapies like mAbs, not all patients' antigens are the same and tumor cells and their antigens mutate. In other words, when the targets change, the targeted vaccine becomes not effective. Moreover, cancer cells used for the development of vaccines contain a high proportion of targets which are not cancer cell-specific, and an improvement of cell surface material is needed to promote the effectiveness of cancer vaccines. Response of "targeted therapies" appears to be around 20 to 30 percent (Active Immunotherapy; Petr *et al.,* 2010). Autologous vaccine therapy being very costly may also cause auto-reactivity and the development of an autoimmune disease. Genetically engineered vaccines may produce neutralizing antibodies, which could cause subsequent therapies with the same product to become ineffiecient. The use of stimulants in poorly immunogenic vaccines may increase immunogenicity of the vaccine, but may also cause increased toxicity

Conclusion

Cancers are most applicable for a therapeutic vaccine approach. Generally, the cancers that are the best applicants are those whose treatments are correlated with high costs and therapies that are not much effective, or all this therapies that affect the risk of many serious side effects for the patient. Cancers such as lung cancer, pancreatic cancer, and breast cancer are such competitors for vaccine therapy. In summary, it is critical that strategies being developed for cancer vaccines be based on clearly defined cellular and molecular targets. We must design rational combinations that act upon several cellular types, including initiators of the immune response (APCs) and effectors cells (T cells). Finally, thoughtful clinical trial design is imperative to evaluate cancer vaccines at this early stage. Given the abundance of concepts coming from the laboratories, the next decade presages unprecedented growth in the development of effective cancer vaccines.

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