Current Concepts In Cancer Vaccines

Kavitha. S.[1], Divya P.D.[2], Rosemol J.M.[3]
[1, 2, 3] Dept of Veterinary Biochemistry
[1, 2, 3] College of Veterinary and Animal Sciences
Kerala Veterinary and Animal Sciences University, Mannuthy, Thrissur, Kerala

Abstract- *Vaccines are antigenic substances prepared from the agents that cause disease and they help to provide immunity. Different types of vaccines and adjuvants that have been investigated for the purpose of controlling cancer. Some of the vaccines such as dendritic cell vaccine and the recombinant viral prostate cancer vaccine, PSA-TRICOM are approved for clinical uses. Different types of cancer vaccines include the vector-based vaccine, peptide vaccine, dendritic cell vaccine, and tumor cell vaccine. Some traditional vaccines are available against those viruses such as HPV virus and Hepatitis B viruses which sometimes cause cervical cancer and some liver cancer. The main function of all these vaccines are the activation of antigen presenting cells and the stimulation of an antigen-specific cytotoxic T lymphocyte-mediated immune response.*

I. INTRODUCTION

Cancer is one of the major causes of death worldwide. Most non-surgical approaches targeting cancerous cells using radiotherapy or chemotherapy also affect normal cells and result in side effects that limit treatment. The rapid increase in knowledge of immune system and its regulation have led to an interest in immunologic approaches to target and eliminate cancer. To take advantage of the immune systems specificity must find antigens that clearly mark the cancer cells as different from host cells. Many potential tumor antigens are not expressed on the surface of tumor cells and thus are inaccessible to antibodies. The immune system has a solution to this problem the MHC antigens (HLA molecules in human) that act as an internal surveillance system to detect foreign substances inside the cell. Monoclonal antibodies have clearly shown therapeutic efficacy in certain cancers most cancer vaccine strategies have focused on induction of cytotoxic T lymphocytes that lyse tumor cells. Unlike infectious disease vaccines, which focus mainly on disease prevention, cancer vaccines have focused mainly on disease treatment. Challenges for cancer vaccines to address are that the immune system in the patient is generally damaged or suppressed not only because of tumor burden but also due to the harmful experience of standard care therapies and advanced age of most cancer patients. Prophylactic and therapeutic vaccine represents one of the most important approaches in the treatment of cancer patient. Theoretically vaccinated patient could mount an immune response able to either cure tumor or keep it under constant restraint.

One of the major problems in developing an efficient cancer vaccine is the lack of tumor specific antigens and the weakness of immune response against tumor associated antigens, usually recognized by the immune system as self-antigens. So various strategies for therapeutic cancer vaccines have been proposed to overcome this weak immune response against tumor associated antigens including cell based vaccine, DNA based vaccine, peptide based vaccine and vector based vaccine. The main function of all these vaccines are the activation of antigen presenting cells and the stimulation of an antigen specific cytotoxic T lymphocyte mediate immune response. The goal of therapeutic cancer vaccine is to teach the patient's own immune system to specifically recognize and eliminate tumor cells. Tumor specific antigens are the ideal target for cancer immunotherapy because of their specificity. Multiple vaccines have been explored in the search for an effective immunotherapy for cancer, but to date only limited success with any one of these has been reported. Each has potential advantages and disadvantages.

II. CANCER VACCINES

Vaccines help to train the immune system to recognize and destroy harmful substances via protecting body from diseases. Treating cancer with vaccines has been a challenging field of investigation since 1950. In clinical investigation the whole cell tumor vaccine has important role and these are personalized vaccine. The main drawback of these vaccines are the limited ability to stimulate immune response (Ribas*et al.,* 2003). The cancer vaccine which either treats existing cancer known as therapeutic cancer or prevent the development of cancer.

Cancer prevention vaccine

Two types of cancer prevention vaccinesare approved by U.S Food and Drug Administration (FDA).

(i) Human papilloma virus vaccine

FDA has approved HPV vaccine to prevent cervical cancer (70%), anal cancer (80%), and vaginal cancer (60%). Approximately 15 HPV genotypes were associated with the development of cervical cancer. When compared with cervical cancer the other cancers attributed by HPV infection are lower rate and so the HPV vaccine is mainly used to target cervical cancer (Schiller and Davies 2004). The vaccines required 2 or 3 doses depending on a person's age and immune system.

(ii) Hepatitis B vaccine

Hepatitis B virus infection is closely related to hepatocellular carcinoma. The first evidence of cancer prevention by vaccination in humans was proved by Hepatitis B vaccine in infant.

Cancer treatment vaccine

Also known as therapeutic vaccine. Vaccines work to boost body's natural defense to fight against cancer. Given to patients already diagnosed with cancer, used for preventing metastasis. The immuno suppressive factors and the negative influence of the tumor micro environment are the major reasons for the limited success of therapeutic cancer vaccine (Schlom*et al*., 2012).

III. CURRENT METHODOLOGIES

1) Vector based vaccine

Vector based vaccine may induce the immune system to generate a strong inflammatory response. This inflammatory response may lead to an increased immune response against the genes that have been inserted into the vector. A number of trials utilizing recombinant viruses expressing tumor antigens; adenovirus, vaccinia, and avipox vectors have been used.

Pox viral vectors are most commonly used in vaccine development. The pox viruses have the ability to accept large inserts of foreign DNA therefore they can accommodate multiple genes. The protype is vaccinia virus which was used successfully to eradicate small pox. The pox virus family is composed of double stranded DNA viruses that replicate within the cytoplasm of infected cells. Other pox viruses have been identified and are currently available for clinical use.

PSA-TRICOM (Prostate Specific Antigen-Triad of CO stimulatory Molecule) also called PROSTVAC is a recombinant viral vaccine that has been developed to treat advanced prostate cancer (Vergati*et al*., 2010). The viral back bone is pox virus sequence (derived from vaccinia or fowl pox). The recombinant fowl pox vector usually generates a weaker immune response in human than vaccinia and is thus often used for booster vaccination after a primary vaccination with recombinant vaccinia. Both vectors contain the prostate specific antigen (PSA) and multiple T cell co stimulatory molecules (LFA-3, ICAM-1 and B7.1 comprising the TRICOM element). Which help to activate host DC and cytotoxic T effector cells then recognize and kill PSA expressing prostate cancer cells.

Over the years several different bacterial and yeast vectors such as Escherichia coli, Salmonella, and Saccharomyces cerevisiae have been investigated for use as vaccine vector.

2) Peptide vaccines

Peptide vaccines are the successful approach for preventing melanoma. Here we use either free peptides or peptides coated on dendritic cells. The use of specific proteins or peptides target for immunotherapy clearly requires a careful choice of the targeted tumor associated antigen and their epitope involving knowledge of their structural and functional characteristics. The short peptide segments composed of 8-10 amino acids fit into a groove in the MHC molecule, combined with the knowledge of the amino acid sequences of tumor epitope, these are able to induce a cytotoxic T lymphocyte response, prompted the use of peptides as therapeutic agents in the treatment of cancer (Berzofsky*et al.,* 2004). Individual peptides will be useful only in patients with appropriate HLA molecules capable of presenting that peptide. Modification of amino acid sequence of epitopes referred to as epitope enhancement. It can improve the efficiency of vaccine through several means,

(i) Increasing affinity of peptide for MHC molecules
(ii) Increasing T cell receptor triggering
(iii) Inhibiting proteolysis of peptide

Peptide is not strongly immunogenic hence fused with certain adjuvant such as cytokines, chemokines and co stimulatory molecule or other immunomodulators that amplify and direct the immune response (Berzofsky*et al.,* 2004). A recent strategy for the development of peptide vaccines uses a synergistic combination of cytokines that induce dendritic cell recruitment (GM-CSF) and co stimulatory molecules that induce dendritic cell maturation. Another adjuvant a CpG-oligodeoxynucleotide (CPG-ODN) characteristic of bacterial DNA is used to elicit a broad range of immune cells. The use of peptide vaccines may be additionally complicated by the choice of adjuvant.

Malignant melanoma is the best studied clinical model of peptide vaccination associated antigen 3 (MAGE A3). It is a peptide cancer vaccine comprised of a peptide derived from the human melanoma antigen A3 with potential immune stimulating and antineoplastic activities. (Berzofsky*et al.,* 2004). Administration of MAGE A3 peptide vaccine to stimulate the immune system and activate the cytotoxic T cell response against tumor cell which expressing MAGE A3 and resulting the tumor lysis.

Immunization with native peptide sequence is often insufficient to generate reactive T cells and clinical response in most patients. Epitope enhanced peptides can generate T cell response but not always clinical tumor responses (Sangha and Butts 2007). Adjuvants including cytokines and co stimulatory molecules improve the immunogenicity of peptide vaccination (Thomas *et al*., 2016).

3) DNA vaccine

DNA based vaccines are a recently developed strategy that has proven capable of activating strong immunity (Vergati*et al*., 2010). DNA vaccine contains DNA that codes for specific antigen from a pathogen. There is no use of using actual infectious organism so these vaccines are safer than the live attenuated which cause pathogenic infection. The DNA vaccines are free from the problems associated with recombinant protein vaccine (Fioretti*et al*., 2010). Provide both humoral and cell mediated immunity. DNA vaccine introduces tumor antigen genes into dendritic cells for endogenous processing without the need for a viral vector. Thus problems of competition from viral vector epitope, reduced efficacy due to prior immunity to the viral vector and potential dangers associated with live virusescan be avoided.

Preparation of DNA vaccine

DNA vaccine composed of bacterial plasmids. Select gene and insert into a plasmid and is transformed into bacteria where bacterial growth produces multiple copies. Then the plasmid DNA is purified from the bacteria. This purified DNA act as the vaccine.

Delivery Methods

(i) Gene gun delivery

It is the simplest method of direct introduction of DNA vaccine into target cells and it is the first described as a method of gene transfer into plants. In this method DNA is coated with gold particles and loaded into the device. Which is similar to the gun and it generates force by which it can penetrate into the cell.

(ii) Electroporation

Injection of DNA this can be assisted by electroporation. For intra muscular electroporation an array of needle electrodes carry an electrical current to the cells in the muscle layer. After an electronic pulse the cell membrane of muscle cell is temporarily permeable allowing DNA plasmid to enter the cell. For the intra dermal electroporation the needle electrodes are introduced into the skin. The DNA plasmids are taken up by the dendritic cell of the skin upon the electronic pulse.

The HPV therapeutic DNA vaccines are considered to using the molecules that are capable to blocking the negative regulators on T cells to enhance the T cell immunity. The combination of HPV therapeutic DNA vaccine with existing forms can leading to the effective control of HPV associated malignancies (Hung *et al*., 2007).

DNA vaccines are very well tolerated with little or no side effects beyond the vaccination site. But DNA vaccines have not yet shown much promise for antitumor vaccination.

4) Dendritic cell vaccine

The professional antigen presenting cells are dendritic cells. Which are the most powerful stimulators of native T cells, because of this dendritic cell are the crucial component of vaccination. For the therapeutic manipulation dendritic cells are attractive target and the complexity of the dendritic cell system require rational manipulation to achieve therapeutic immunity (Banchereau and Palucka 2005). Dendritic cell based immunotherapy is safe and can promote anti-tumor immune response and prolonged survival of cancer patients. When dendritic cell encounter inflammatory mediators such as bacterial lipopolysaccharides and tumor necrosis factor alpha, them they become mature. Helper T cells also induce dendritic cell maturation via CD40 ligand interaction with CD40. The combination of dendritic cells with activated T cells were injected into malignant effusion can induces the long term disease stability even in patients have resistance for chemotherapy (Morisaki et al., 2003).

The cells (immature dendritic cell) from body grown with tumor lysates or inactive tumor cell from patient, antigenic peptide and vector that carries antigenic peptide, this gives a set of mature dendritic cell that displays the tumor antigen on their surface and are ready to activate other immune cells. These mature dendritic cells injected into

patient it activate other immune cells and destroying tumor cells. When the dendritic cell subset is targeted with a vaccine different receptors were expressed and these receptors can deliver different signals to the same dendritic cell which able to initiate distinct type of immune response (Palucka and Banchereau 2013).

Sipuleucel-T (provenge) is an autologous dendritic cell vaccine used to treat prostate cancer, which is the first therapeutic cancer vaccine approved by the U.S food and drug administration (Cheever and Higano 2011). It is generated by modified patient derived dendritic cell to express a fusion protein comprised of prostatic acid phosphatase (PAP) and granulocyte macrophage colony stimulating factor (GM-CSF) which provide maturation factor for the dendritic cell. At first patient cells are collected and a leukapheresis method is used to extract the antigen presenting dendritic cell they are co incubated with the fusion protein which is taken up, processed and presented on the cell surface. In this activated antigen presenting state the dendritic cells are then returned to the patient to generate an immune response. Three courses of treatment are administrated over a period of 6 weeks to trigger an immune response against PAP positive prostate cancer cells.

5) Tumor cell vaccine

The richest source of antigen is the tumor cell itself. However use of autologous tumor cell vaccine (patient himself) is cumbersome to large scale vaccine production and tumor samples are often unavailable. Approaches uses Allogenic (some other patient with similar cancer) are more widely applicable. A number of genetically modified Autologous or allergenic tumor cell vaccines have been tested in clinical trials. OncoVAX (vaccinogen) is composed of autologous irradiated tumor cells with or without an adjuvant. (Vergati*et al*., 2010).

The cells are genetically modified to produce certain immune molecules that will trigger an immune response against the tumor and then inactivated using chemicals or radiation so that they cannot form a tumor. Such modified tumor cells are injected into the patient intravenously. The tumor cells are encountered by the antigen presenting cells there by triggering a cascade of tumor education of the immune cells and tumor destruction. (scanlan*et al*.,2001).

IV. SIDE EFFECTS

Cancer vaccines have some side effects. The most common side effects are inflammation at the site of injection including redness, pain, swelling and occasionally a rash, sometimes flu like symptoms including fever, weakness, dizziness, nausea, muscle ache and headache. These effects are usually last for only short time.

V. LIMITATIONS

1. Suppress the immune system ; we use adjuvants in vaccine to fix this problem
2. Cancer cells develop from a person's own healthy cell; the cancer cell may not look harmful to the immune system it may ignore the cells instead of finding and destroying them.
3. Larger or more advanced tumors are hard to get rid of using only vaccine; this is one reason why doctor often give patients cancer vaccine with other treatment.
4. The older or sick people can have weak immune system and their body may not be able to produce a strong immune response after vaccination so it limits how well a vaccine works.

VI. CONCLUSION

As prophylaxis against acute infectious diseases, vaccines have been among the most cost effective agents, saving many millions of lives. For treatment of cancer, vaccines have yet to achieve widespread success. The generation of vaccine holds promises to control or cure cancer. More research still need to overcome hurdles in the making of these vaccines. Most importantly the vaccines could mean better quality of life and longer survival of patient.

REFERENCES

[1] Banchereau, J. and Palucka, A.K. 2005. Dendritic cells as therapeutic vaccines against cancer. *Nat. Rev.Immunol.* **5**: 296.

[2] Berzofsky, J.A., Terabe, M., Oh, S., Belyakov, I.M., Ahlers, J.D., Janik, J.E. and Morris, J.C. 2004. Progress on new vaccine strategies for the immunotherapy and prevention of cancer. *The J. of clin.investigation*, **113**:1515-1521.

[3] Chang, M.H., 2009. Cancer prevention by vaccination against hepatitis B. In *Cancer Prevention II* ,85-94.

[4] Cheever, M.A. and Higano, C.S., 2011. PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. *Clin. Cancer Res.***17**: 3520-3526

[5] Fioretti, D., Iurescia, S., Fazio, V.M. and Rinaldi, M. 2010. DNA vaccines: developing new strategies against cancer. *BioMed. Res. Int. 2010*.

[6] Hung, C.F., Monie, A., Alvarez, R.D. and Wu, T.C. 2007. DNA vaccines for cervical cancer: from bench to bedside. *Exp. & mol. med.* **39**:679.

[7] Morisaki, T., Matsumoto, K., Onishi, H., Kuroki, H., Baba, E., Tasaki, A., Kubo, M., Nakamura, M., Inaba, S., Yamaguchi, K. and Tanaka, M. 2003. Dendritic cell-based combined immunotherapy with autologous tumor-pulsed dendritic cell vaccine and activated T cells for cancer patients: rationale, current progress, and perspectives. *Human cell*, **16:**175-182.

[8] Palucka, K. and Banchereau, J. 2013. Dendritic-cell-based therapeutic cancer vaccines. *Immunity*. **39**:38-48.

[9] Ribas, A., Butterfield, L.H., Glaspy, J.A. and Economou, J.S. 2003.Current developments in cancer vaccines and cellular immunotherapy. *J. of clin.Oncology*. **21**:2415-2432.

[10] Sangha, R. and Butts, C. 2007. L-BLP25: A Peptide Vaccine Strategy in Non–Small Cell Lung Cancer. *Clin. Cancer Res. **13**:*4652-4654.

[11] Scanlan, M.J. and Jäger, D. 2001. Challenges to the development of antigen-specific breast cancer vaccines. *Breast Cancer Res.**3**:*95-98.

[12] Schiller, J.T. and Davies, P. 2004. Delivering on the promise: HPV vaccines and cervical cancer. *Nat. Rev. Microbiol.**2**:*343.

[13] Schlom, J. 2012. Therapeutic cancer vaccines: current status and moving forward. *Journal of the Nati. Cancer Inst.* **104**:599-613.

[14] Thomas, S. and Prendergast, G.C. 2016. Cancer vaccines: a brief overview. In *Vaccine Design* .755-761.

[15] Vergati, M., Intrivici, C., Huen, N.Y., Schlom, J. and Tsang, K.Y. 2010.Strategies for cancer vaccine development. *BioMed.Res. Int. Research International*.