WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 14, 1544-1553. Review Article ISSN 2277– 7105

AN OVERVIEW OF CURCUMIN AS ADJUVANT IN CANCER VACCINES

K. Yogeswaran[1*], B. Vanitha[2], S. Divya Lakshmi[3], A. Monica[4] and O. Silpa[5]

School of Life Sciences, JSS Academy of Higher Education and Research, Ooty Campus, Long Wood, The Nilgiris.

Article Received on
19 October 2021,

Revised on 09 Nov. 2021,
Accepted on 29 Nov. 2021

DOI: 10.20959/wjpr202114- 22467

***Corresponding Author**
K. Yogeswaran
School of Life Sciences, JSS Academy of Higher Education and Research, Ooty Campus, Long Wood, The Nilgiris.

ABSTRACT

Cancer is a disease that caused most deaths among people. Various treatments against cancer are present these days. A new way of cancer treatment has arisen in the field of oncology that is cancer vaccines. Cancer vaccines prevent cancer and are also used to treat existing cancer. There is various adjuvant used along with the vaccine. This review aims to introduce the different modes of action of adjuvant and give insight into the types of adjuvant that possess the greatest potential for adjuvanticity. Curcumin is one of the best options that can be used as an adjuvant. Curcumin combined with the FAPαc vaccine, IDO expression, and TNF-α-induced EMT can be inhibited. Curcumin with Listeria^{AT}-mage-b increases the efficacy against metastases in TNBC model 4T1 through a reversal of tumour-induced immune suppression. Curcumin micelles would remodel the tumour microenvironment to improve the efficiency of the vaccine in which curcumin polyethylene glycol conjugate (CUR-PEG) and is effective in immunotherapy of melanoma. The final review shows that curcumin can be used as an adjuvant for cancer vaccines. Curcumin can also boost the treatment for cancer along with cancer vaccines.

KEYWORDS: Cancer, Cancer vaccine, Curcumin, Adjuvant.

INTRODUCTION

Cancer is a group of diseases responsible for 12% of deaths globally. The third most common cause of death accounts for 9.5% of all deaths. According to GLOBOCAN (WHO), there are above 12.7 million persons diagnosed with cancer during 2008. Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. Cancer is a disease where

cells grow out of control and invade, erode and destroy normal tissue. There are about 200 different types of cancer. It can start in any type of body tissue. Cancer can occur at any age, but 67% of cancer deaths occur in people older than 65 years. Cancer treatments may include chemotherapy, radiation, surgery, targeted cancer treatments, small molecule inhibitors, antibodies, cell-based immunotherapy, gene therapy, hyperthermia, stem cell transplant, photodynamic therapy, laser treatment, blood donation, and transfusion. Vaccine development is one of the most promising and exciting fields in cancer research; numerous approaches are being studied to develop effective cancer vaccines. Cancer vaccines aim to stimulate the immune system to be able to recognize cancer cells as abnormal and destroy them. The cancer vaccine is a medicine that belongs to a class of substances known as biological response modifiers. Biological response modifiers work by stimulating or restoring the immune system's ability to fight infection and diseases. Recent studies have shown that curcumin can be used as an adjuvant for cancer vaccines which results in increases the efficiency of the vaccine. Curcumin is a great remedy as an anti-cancer and antitumor agent.

VACCINES

Vaccines are a biological product that activates your immune response to a specific disease to fight against the disease and protection from that disease. A vaccine to a specific disease contains the disease-causing organism itself either inactivated (killed) or live attenuated (weakened). The organisms are killed by heat, formalin, phenol, and alcohol.[1] The action of vaccine will be by mimicking the natural interaction with the human immune system. The vaccine reduces the risk of complications and mortality even after exposure to that specific disease. Most vaccines are given by parenteral injection and it will induce systemic immune responses expressed by B cells and T cells.[2] Many immunization programmes are employed all over the world particularly focusing, on pregnant ladies, infants (below 5 years) and children, because they are at high risk of diseases preventable by vaccines.[3]

ADJUVANT

An adjuvant is a drug or other substance or a combination of substances, that is used to increase the efficacy or potency of a certain drug. The potency of poorly immunogenic antigens is enhanced by including adjuvant in sub-unit or recombinant vaccines.[4] There is various type of adjuvants available like alum, MF59, MPL, AS04, AS01B, and ASO2A, virosomes, TLRS, Alum salts works on many pathways, which doesn't depend on TLRs signalling. These adjuvants enhance an antigen-specific immune response in vivo. Due to the

weaker immunogenicity of subunit vaccines adjuvants are added to stimulate the immunogenicity. Vaccines need entities like adjuvants to boost the immunogenic responses of the specific antigens. Adjuvants may exert their immune-enhancing effects according to five immune functional activities: -

1. Translocation of antigens to the lymph nodes where they can be recognized by T cells.
2. Antigen protection enables longer exposure.
3. Enhanced local reaction at the injection site.
4. Induction of the release of inflammatory cytokines.
5. Interaction with PRRs, specifically TLRs.[5]

They are more important in increasing the potency and efficacy of vaccines. A deep study of different adjuvants and their functions would help in finding novel adjuvants.[6] Many studies are conducted to study the role and functions of different adjuvants. However, only a few adjuvants are used for vaccines.

CURCUMI (The Indian solid gold turmeric)

Curcumin ($C_{12}H_{20}O_6$) is extracted from turmeric which is derived from the rhizome of the plant *Curcuma longa*. Curcumin is an orange-yellow crystalline powder extracted from turmeric in the amount of 2-5% present in the whole spice. It is called in other names as Indian saffron, yellow ginger, yellow roots, Kacha Haldi, Yukon, or natural yellow 3. Chemically been Diferuloylmethane. It is insoluble in water and soluble in organic solvents. During phase I clinical trials higher doses like 12g/day have shown poor bioavailability in humans.[7] Curcumin decreased UV-induced inflammation, apoptotic changes in human keratinocytes and dermal fibroblasts, and the expression of matrix metalloproteinase.[8] Curcumin potentialities have continuous proliferation, escaping apoptosis, continuous angiogenesis, insensitivity to growth inhibitors, tissue invasion, and metastasis.[9]

Scientific classification of turmeric

Kingdom - Plantae

Order - Zingiberales

Family - Zingiberaceae

Genus - Curcumin

Species - Curcumin longa

CURCUMIN CHEMICAL COMPOSITION

- Melting point 183^0c
- Molecular formula $C_{12}H_{20}O_6$
- Molecular weight: 368.37 g/mol
- Turmeric contains curcumin along with other constituents known as “curcuminoids”.
- Major constituents: - curcumin 50-60%, essential oils 2-7% with high content bias borane derivatives.
- It also contains Desmethoxycurcumin (DMC), Bisdemethoxycurcumin (BDMC), common phytosterols, Ar-turmerone, Zingiberene fatty acids, and polysaccharides.

CANCER VACCINE

Cancer vaccines are known as biological response modifiers. These biological response modifiers will improve the ability of our immune system.

Two types of cancer vaccines: -

- **Preventive (or prophylactic) vaccines**

Protects people before developing cancer in their body.

- **Treatment (or therapeutic) vaccines**

Helps and improve our own immune system to fight against the existing cancer in our body.

There are many treatments for cancer in the present day: -

1. Using specific antigens produces monoclonal antibodies and treats against those specific antigens.
2. For releasing the "breaks" of T cells immune checkpoint blockade (ICB).
3. With the help of the patient's autologous cells, chimeric antigen receptor (CAR) T cell therapy is done.
4. Oncolytic viruses selectively kill cancer cells.
5. Few immunotherapeutic cancer vaccines are available commercially such as anti-CTLA4, anti-PD1, and anti-PD-L1, CAR- T cells against acute lymphoblastic leukemia and B cell lymphoma.

CELL-BASED CANCER VACCINE

Antigens such as foreign bodies and self-tumour cells provoke an immune response, as specialized immune cells called **Dendritic cells** play a major role in the immune response.

Dendritic cells act as boosting a memory T cell response and they are effective initiators of naive T cell responses.[10]

The activity of the tumour-cell-intrinsic pathway is linked to genetic alterations and targeting of tumour-cell-extrinsic factors, such as growth factors, which leads to the development of novel cancer vaccines development.[11]

Over a century ago, it was reported that immunization with embryonic/fetal tissue could lead to the rejection of transplanted tumours in animals. Animal studies should that vaccination of embryonic/fetal tissue induces humoral and cellular immunity against transplantable tumors and carcinogen-induced tumours. The oncofetal antigen-based cancer vaccine using autologous induced pluripotent stem cells (iPSCs) has shown marked prophylactic and therapeutic potential, suggesting critical roles of oncofetal antigens in inducing anti-tumour immunity.[12]

GENE-BASED CANCER VACCINE

DNA CANCER VACCINE

To activate our immune system against cancer therapeutic DNA cancer vaccines are a very promising technique used in present days. The tumour develops immunosuppressive mechanisms in which the DNA cancer vaccine develops only modest therapeutic effects in clinical trials. There are two different strategies are employed for the DNA cancer vaccine to enhance the immune response and the treatment efficacy of the DNA cancer vaccine.[13]

RNA-BASED CANCER VACCINES

RNA vaccines are made by using messenger RNA synthesized by in vitro transcription, bacteriophage RNA polymerase, and template DNA that encodes the antigen(s) of interest are been used. To stimulate an immune response the antigens are presented to the antigen-presenting cells by the mRNA transcripts are translated directly into the cytoplasm. To elicit a specific immune response loading either tumour-associated antigen mRNA or total tumour RNA into dendritic cells and deliver to the host body. It is important to recognize that mRNA-encoded products are degraded by proteasomes and presented on MHC class I molecules to CD8+T cells and do not reach the MHC class II processing pathway to induce CD4+T helper cell responses. The translation occurs in the cytoplasm, to transfect a cell the RNA gains entry into the cytoplasm. Also, RNA has no oncogenic potential RNA cannot integrate into the genome.[15]

CANCER VACCINE ADJUVANTS

To increase the effectiveness of the vaccine on effector T cells immunostimulatory adjuvant is used. Along with the cancer vaccines another plasmid or injected as protein. IL-2, IL-12, and GM-CSF, IL-2 is the some of the adjuvant used which are involved in differentiation of immature T cells into effector T cells. Recent studies also suggested that other adjuvants can be used to increase the efficiency of cancer vaccines such as INF γ, IL-15, IL-7, TLR-activators.[14]

EFFICACY OF CURCUMIN AS ADJUVANT IN CANCER THERAPY

Turmeric (Curcuma longa) is a popular spice that has been used in Ayurvedic medicine for its ability to treat various common ailments. There have been statistical correlations between turmeric consumption and lower incidences of cancer development, prompting research into its primary component curcumin. Several in vitro and in vivo studies over the last decade into cancer treatment have provided experimental evidence that curcumin contains antiproliferative, antiangiogenic, and apoptotic properties. Curcumin capsules or placebo was given orally for the patient with active mild to moderate ulcerative colitis. The capsule contains 3g of curcumin which is administrated per day. The capsules or placebo were randomly assigned as curcumin enema (NCB-02) plus oral 5-ASA or placebo enema (NCB-02) plus oral 5-ASA once daily. The final study showed 43.4% remission in the curcumin group compared to 22.7% in the placebo group and also 56.5% clinical response in the curcumin group and 36.4% in the placebo group.[16]

CURCUMIN COMBINED WITH FAPαc VACCINE

Fibroblast Activation Protein (FAPαc) is a potential target for cancer therapy. By using TNF-α it can induce EMT. The activate secretion of IFN-y and IFN-a will be done by elimination of FAP-a + fibroblasts. IFN-y can in turn induce expression indolamine-2, 3-dioxygenase (IDO). By these two effects, the tumour vaccine limits are limited. Studies show IDO expression and TNF-α-induced EMT can be inhibited by the combination of curcumin. Also, curcumin inhibits the growth of the tumour and increased the survival of mice which is introduced with melanoma cells. So, the final results show curcumin and FAPαc vaccine combination is showing improved results in melanoma therapy.[17]

CURCUMIN WITH LISTERIA^{AT} – MAGE – B VACCINE

There is a hypothesis that IL-6 reduction may improve the efficacy of vaccination against TNBC cancer through improved T cell responses. To test this hypothesis combination of

Listeria^{AT} –mage-b vaccinations and curcumin after tumour development hence curcumin is consumed all over the world. The study shows that curcumin significantly improves the therapeutic efficacy of Listeria^{AT}-mage-b with both immunization strategies particularly against metastases in a TNBC model 4T1. The study shows that curcumin improves the efficacy of Listeria^{AT}-mage-b. Vaccine against metastases in TNBC model 4T1 through the reversal of tumour-induced immune suppression.[18]

CURCUMIN MICELLES REMODEL TUMOR MICROENVIRONMENT

The hypothesis was that curcumin would remodel the tumour microenvironment to improve the vaccine activity in which curcumin polyethylene glycol conjugate (CUR-PEG), an amphiphilic CUR-based micelle, was delivered intravenously to the tumor. By the study B16F10 tumour-bearing mice, the combination of CUR-PEG and vaccine treatment resulted in a synergistic anti-tumour effect compared to individual treatments. In vivo cytotoxic T-lymphocyte response and interferon-γ production are increased significantly with combination therapy of CUR-PEG inside immune organs. By the study of the tumour microenvironment, the combination therapy significantly downregulated levels of immunosuppressive factors, such as decreased number of myeloid-derived suppressor cells and regulatory T cells and declined levels of IL-6 and chemokine ligand 2 in correlation with increased levels of proinflammatory cytokines, including tumour necrosis factor-α and IFN-γ as well as an elevation in the $CD8^+$ T cell population. Down-regulated signal transducer and activator of transcription 3 pathway are observed in the combination of CUR-PEG and vaccine. The study results show the CUR-PEG is effective in the immunotherapy of melanoma.[19]

CONCLUSION

A plan for the diagnosis and treatment of cancer is a key component of any overall cancer control plan. The development of cancer vaccines and immunotherapy has given hope for the cure of cancer and cancer prevention. Curcumin as a natural gift serves as an anticancer or anti-tumour remedy for centuries. So, studies show that by using curcumin as an adjuvant in cancer vaccine and immunotherapy the efficiency of the treatment and suppressing the tumour is significantly improved. Also, curcumin is economically easily available it can be used in the future in the development of cancer vaccines.

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