

The future of immunotherapy in cancer



1. Introduction

Cancer diseases are implicated to be the second cause leading to the death in the world. Thus, from long time there were some questions have been raised in order to understand the molecular basis of the main reasons behind it and then find the suitable treatments. These questions involved; do cancer cells displays tumor-specific antigens, can the immune system distinguish these antigens and if yes, what is their nature and why are they not being targeted? [2] Indeed, through t he last 110 years it has been seen that an evidence to support the observation that both of the innate and adaptive immune responses can recognize and eradicate tumors towards cancer immunotherapy. However, there are a number of intrinsic difficulties in cancer, such as the antigenic similarity between the tumor and normal cells, the rapid proliferation of tumor cells and their reduced immunogenicity [3, 4]. To overcome these issues, scientists have designed ways to enhance the immune system to distinguish cancer cells and increase its response to destroy the cancer. Recently, there are two main types of cancer immunotherapy strategies have developed and these include passive and active approaches that aim to elicit cancer cells. Passive immunotherapy riles on the use of specific monoclonal antibodies that used alone or in correlation with radioactive cytotoxic agents and substances or adoptive transfer the lymphocyte against tumor antigens and also manipulating other effectors cytokines such as interferon-alpha and this field gave successful results against fight cancer . Active immunotherapy depend on enhance of the immunogenicity of tumors during the induction of cytokine production in addition to gene expression. [4, 5]. The main aim of this essay is to discuss

some recent data about the current prospects for improved cancer immunotherapy and try to understand how could improve the efficacy of the therapy in near future.

2. Tumor antigens:

Tumor cells can be distinguished from normal cells by quantitative and qualitative differences in their antigens . Thus; it can be classified based in their nature (table . 1).

3. Immune response to tumors:

The immune system can defend the host cell from virus-induced tumors by eliminating or suppressing these viruses in addition to make quick resolving the inflammatory environment and then prevent creation of tumorigenesis . Furthermore, It can specifically identify and eliminate tumor cells on the basis of their expression of tumor-specific antigens or molecules induced by cellular stress before they can cause harm and this is known as immune surveillance [7] . In addition, it has been suggested that NK cells able to kill the cells that have lost the MHC class I . As a result, cancer cells are attacked by the NK cells due to the lack of the expression MHC-1 at their surfaces.[8] Moreover, the NK cells cell facilitates mediate the antibody dependent cell-mediated cytotoxicity (ADCC) by binding the FC receptor with tumor cells . Also, macrophages play an important role when they activated by IFN-gamma and macrophage activation factor (MAF), and that because they can inhibit growth the cancer cells through secretion of the lyric enzymes.(figure 1) [9]However, some scientist has found that the immune not always can demolish the cancer cells. Thus, some cells escape from the immune system and develop the cancer. (figure2)

Figure 1:” immune responses to tumour antigens. Activation of pre-cytotoxic CD8C T cells depends on recognition by the T-cell receptor of a specific epitope presented by an MHC class I molecule on the tumour cell. Cytokines secreted by CD4C cells directly influence T-helper differentiation and provide further stimulatory signals for pre-cytotoxic CD8C T cells. Alternatively, tumour antigens are taken up by antigen-presenting cells , which are able to activate T-helper cells or prime pre-cytotoxic CD8C T cells”. Taken from (6).

Figure 2. “ Mechanisms of tumor-cell escape from immune-mediated control. Tumor cells can escape from immune system-mediated control through different mechanisms: 1) loss of expression of HLA-I molecules result in impairment of T cell-mediated recognition; 2) loss of adhesion molecules, such as ICAM1, the counter receptor of LFA1, or CD40, can render tumor cells less susceptible to cytolytic effector cells; 3) tumor cells can also release soluble factors, such as TGF- β^2 and IL-10, that have a role in the direct immunosuppressive effect on T cell proliferation or these cytokines are important for the generation of CD4+CD25+ regulatory. Cells (Treg) which are effective at 1: 1-1: 10 Treg: responder cell ratios and express CTLA4 and GITR besides the transcription factor Foxp3; 4) tumor cells can release MIC-A and ULBP1-4, which are the counter -ligands of NKG2D activating receptor, resulting in blocking NKG2D activation of cytolytic effector cells; 5) the release of sFasL by tumor cells by interacting with Fas expressed by anti-tumor effector cells can induce their apoptosis”. Taken from (10).

4. Current cancer immunotherapy

4. 1. Passive immunotherapy

This type of strategies involves of specific monoclonal antibodies or other components of the immune system which are designed out of the body and managed to patients to offer them immunity against target disease or fighting the infection. This approach of immunotherapy not depends on the stimulation of the immune response like the way that vaccine dose. [11. 12]

Monoclonal antibody therapy (mAbs)

Today, the treatment using monoclonal antibody become most common form of cancer immunotherapy and that because the ability of these antibodies to spare normal cells and bind specifically towards the antigens present on the surfaces of cancer cells and then kills these cells . Moreover, the efficacy of these antibodies will be increased as a result of discover the specific cancer associated antigen that lead to raise the specificity of these antibodies. Recently, there are two main types of monoclonal antibodies are used as therapy in cancer. Naked monoclonal antibodies which are free from any substances attached with it such as drug or radioactive substance . The second type that is associated with the chemotherapy drug, toxins or radioactive material which called conjugated or tagged monoclonal antibodies.[11, 12]. Conjugated mAbs convey the treatment in a straight line to the cancer cells, thus it has restrictive to harm healthy cells, even though these are more effective comparing to naked mAabs, and they are as well correlated with additional side effects due to the attached materials [12]. Despite the grate successful outcomes in the treatment of cancer using monoclonal antibodies, there are some limitations have been observed .

Because mAbs use after chemotherapy and radiation , thus they have narrow effectiveness as a result of cancer mutate. Also, not all the patient's cancer have the same antigens since mAbs are specific targeting one antigen.(table. 2)

4. 2. Active immunotherapy

4. 2. 1. Cancer vaccine

Unlike the protection vaccine that are used before occurred the infection, cancer vaccine is given for the people who have already cancer in order to enhance their immune system to struggle with the cancer cells. These vaccines are attached with some specific tumor antigens that help the immune system to recognize the cancer target cells. In general, cancer vaccines follow two groups either cell based or vector based (an engineered virus): In terms of cancer vaccine based from cells, vaccine is created from the patient cancer itself and then returns it back using some cytokines such as IL-2 that will activate the immunity of cellular antitumor. With regarding to the vaccine based from vector (virus), it is aimed to introduce the specific proteins taken from the cancer cells and given to the patients for stimulating the immune system. Generally, both of the two approaches are created to induce the immune system against the cancer cell [15]. (table. 4). Although cancer vaccines have afforded promising results in the treatment of the cancer, there are some shortcomings have been noticed (table 5).

Vaccine

Mechanism of Action

Antigen/adjuvant

<https://assignbuster.com/the-future-of-immunotherapy-in-cancer/>

Uses specific protein fragments or peptides to stimulate the immune response to fight tumor cells.

Whole cell tumor

Uses whole tumor cells that contain cancer antigens taken from the patients with cancer (autologous) or from another person (allogenic) to stimulate immune response.

Dendritic cell

Uses specialized white blood cells (dendrites) from the patient's to stimulate the patient's own cancer antigens

Viral vectors and DNA

Uses nucleic acid sequence of the tumor antigens to produce cancer antigens proteins that stimulate immune response to attack tumor cells containing the same antigen.

Idiotype

Uses antibodies produced by certain cancer cells; these are unique to each patient and can trigger an immune response similar to antigen vaccines.

Table 4: Some examples of the types of therapeutic cancer vaccines including a brief description the mechanism of action. Take from (16).

Type of vaccine

Advantages

<https://assignbuster.com/the-future-of-immunotherapy-in-cancer/>

Disadvantages

Allogeneic cellular

Simple to prepare and broad spectrum of potential antigens

Irrelevant “ allo” antigens, difficult to precisely characterize components ,
and requires adjuvant

Autologous cellular

Patient-specific unique antigens and presents numerous antigens

Custom-made individual vaccine production and requires adjuvant

Autologous heat shock proteins

Patient-specific unique antigens and presents numerous antigens

Custom-made individual vaccine production, production can be difficult

Purified protein or carbohydrate

Well-defined components, safety, and immunogenicity established

(carbohydrates) in mature clinical trials

Production can be difficult and requires adjuvant

Peptide

Simple to prepare and safety established in early trials

Single epitope, HLA-restricted, and requires adjuvant

Dendritic cell

Inherently immunogenic and potentially numerous epitopes

Production can be difficult and limited epitopes and HLA restriction when used with peptides

Recombinant virus

Inherently immunogenic and numerous epitopes

Neutralizing immunity to vector

DNA

Simple to prepare, numerous epitopes, and immuno-stimulatory sequences in vector

Little clinical data to date

Table 5: Some of the advantages and disadvantages of different type's cancer vaccines. Taken from (17).

4. 2. 2. Cellular therapy

Cell immunotherapy includes use a specific cell derived from the cancer patient itself that developed in the vitro in order to increase their immune response for recognizing and killing the cancer cells and then return it again using some types of cytokines such as IL-2 and IL-12 and other co-stimulatory molecules in order to inducer their immune response to kill the cancer cell. [6]

Interleukin-2 (IL-2):

It is an important factor for T cells proliferation; also it can improve the function of natural killer (NK). In addition, it able to activate the lymphokine-activate killer (LAK) cells that cable of damage cancer cells and enhance sustain of the immune function. Thus, it has been seen that when Il-2 administrated alone or associated with patient lymphocytes to treat melanoma and renal cancer, would give promising results [18]. However, current studies have shown that, treatment with Il-2 can lead to increase the toxicity due to increase the production of other cytokines and their accumulation in the body, in addition to increase the self tolerance that result in autoimmune disease [19].

Interleukine-12 (IL-12):

IL-12 plays an important role in production of interferon gamma (IFN- $\hat{\beta}$) and the progress of a Th1 type immune response, thus playing a role in both innate and adaptive immunity. It has been found that in mouse modules, IL-12 can restrain tumor growth and metastasis . However, induce the production of IFN- $\hat{\beta}$ may lead to increase the toxicity that affect to the innate resistance mechanism.[20]

5. How could improve the strategies of the current immunotherapy?

Using vaccines derived from antigen associated with dendritic cells or on combination of tumor specific peptides with potent adjuvants such as toll-like receptor (TLR) agonists are potent stimulators of the immune response [22 - 23HYPERLINK “#bib80”-24]. As known, vaccination aimed to induce immune

response of T cells to recognize the antigenic peptide of the tumor cell that are generated in the proteasome and then presented in the course of MHC class- I. However, not all the cancer cells can present one peptide during degrading by the proteasome. It has been seen that, some cancer cells such as melanoma can produce two peptides after breaking down via the proteasome that are not adjacent in the main protein. [25]. Therefore, to overcome this issue it necessary to develop vaccine contains multiple antigens (epitopes) in order to reduce the possibility of the cancer cell from producing some peptides that do not display particular antigens. On the other hand, there was issue has been noticed with use the multiple antigens, it appears to have low stability to response for the tumor antigens peptides. This problem may be dissolved by using more stable peptides. Nevertheless, these peptides could stimulate specific response of T cells that do not discriminate the main peptide [27-28]. Furthermore, we can induce the immune response by attaching the specific tumor peptides to Toll Like Receptor (TLR) in order to improve the antigen presentation by DC for intracellular peptides[28].

Additionally, we can produce other antigens used as DNA chain or RNA for direct expression in antigen presenting cell (APC) [29]. Furthermore, in vivo , it has been shown that dendritic can be targeted directly by use fusion protein of antibody antigen that are specific for DC surface receptors and then lead to induce immunity for antigen specific peptides [30]. Because of the cancer cells able to rebuild itself, thus may be a big challenge of developing an efficient vaccine [31]. As a result, it has been revealed that

DCs associated by means of transformed stem cell like glioma cells offered successful outcomes in mice [32].

Another approach to improve immune response for specific tumor can be achieved by avoid DC from inhibition by the cancer cell through generating inflammatory environment within the site of tumor . It has been exposed that when melanoma cells infected with *S. typhimurium*. This can lead to killing of infected cancer cells[103]. As the tumor immunosuppression is vital mechanism to establish the cancer, thus there are two main approaches are designed to prevent produce of immune inhibitory mediators . One aimed to eradicate the mediators of the tumor immunosuppression through change the cytokine and chemokine of the tumor cells, while the second mainly aimed to eliminate other immune cells that lead to activation of T cell. In the first, it has been seen that the importance of Indoleamine 2, 3-dioxygenase (IDO) in activation of the tolerance. This enzyme is produced by many cells such as DC and tumor cells as well . this enzyme is controlled by tumor suppression gene (*bin1*)[34].

However, not all the cancer cells express this gene such as prostate cancer [35]. To improve the efficiency of the cancer vaccines, it has been found that the correlation inhibition of IDO with engagement with TLR through vaccination may lead to improvement of T cell activation. Also, recent studies have shown that, chemotherapy can develop the effects of immunotherapy by means of induce immune cell through binding with tissue necrosis leading to release the danger signals that can facilitate presentation of the tumor antigens to recognize by immune cells. [36]. Also, it has been

suggested that, when chemotherapy associated by lymphodepletion can lead to elimination of T regulatory cells (table 6).

Another way to improve immunotherapy is use low doses of radiation that able to damage cancer cells due to shrink the cancer cell and then can be removed by surgery. For example, in prostate cancer it has been shown that radiotherapy can make easy for cross-presentation of the tumor antigen. (table 7).

Furthermore, recent studies have found that triggering the host anti-tumor immunity using gene therapy is very promising approach to improve the immunotherapy [37] in the course of the use of RNA interference to treat tumor by curtail mechanisms that attenuate the host immune response.[38]

“ The immune system of cancer-bearing individuals suffers from tumor-induced tolerance, which should be alleviated (Step 1) before induction of an active immune response with tumor vaccines (Step 2). Some evidence suggests that prior vaccination (Step 2) favors the antitumor effects of chemotherapeutic agents (Step 3). Cell death triggered by chemotherapy or radiotherapy (Step 3) should then be rendered immunogenic via addition of compounds that enhance calreticulin expression at the tumor cell membrane (Step 4). To overcome putative TLR4 host defects, which can compromise the developing immune response, administration of chloroquine is indicated (Step 5). Finally, immune adjuvants should be given to sustain and enhance the ensuing antitumor immune response (Step 6). Potential mediators at each step are listed. GMTV, genetically modified tumor vaccines; PP1-

GADD34, protein phosphatase 1 complexed to GADD34; IL-15 sushi, sushi domain of soluble IL-15 receptor $\hat{\pm}$ (99).” Taken from (39).

6. Conclusion and future directions:

Increase our knowledge in understanding how the cancer cells can evade from the immune response has lead to develop two approaches of the immunotherapy active and passive strategies. However, there were some limitations that have been detected with those strategies in terms of their cost and side effects. Recently, it has been seen that combination of active and passive (comprehensive) has gave great promise. Moreover, it has been found the stimulating of the host immune response using gene therapy in combination with specific cytokines, co- stimulatory molecules, sensitized antibody are seen to become a potent factors to overcome the previous attempts does not offer it. However, In future, a lot of intensive researches required in a way of that how can we create an efficient vaccine that deliverer by intelligent delivery system and offers great results without side effects.