BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, December 2014. Vol. **11**(3), 1167-1178

Immunotherapy as an Optimal Manner in Cancer Treatment (Review Article)

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doi: http://dx.doi.org/10.13005/bbra/1502

(Received: 06 September 2014; accepted: 15 October 2014)

Cancer is one of the main causes of mortality in worldwide. When the normal cell division and growth is distorted or on the other hand, the normal cell cycle control processes, which normally occur, are destroyed, the cells will be cancerous. In the event that these cells migrate to other places are known as malignant cancer. Scientists use different methods to treat cancer, such as surgery, chemotherapy, laser therapy. These methods may also cause damage to healthy cells. For this reason, a method is optimal for this purpose as it can involve the least side effects. Immunotherapy is a method in which abnormal cells are Identified and destroyed. Since the immune system is used as the major part in immunotherapy, it is an appropriate method for the purpose. The cancer cells can be detected by immune system and appropriate responses can be taken to them since they induce modifications on the surface, or display their specific antigens. Accordingly, the vaccines can be constructed by which the body will be resistance against cancer. Antigens, especially cancer-specific epitopes are important in vaccine developing. Nowadays scientists have developed several vaccines on this basis, including vaccines against prostate and breast cancers. In this study, we studied various methods of cancer treatment, and then studied the immunotherapy as optimal method in cancer treatment. Ultimately various methods of tumor escape from the immune system will be discussed.

Key words: Cancer, Immunotherapy, Optimal manner

Today, cancer is one of the most important factors of death in worldwide. Tumors are resulted from uncontrolled division in normal body cells. Cell cycle is normally regulated by a family of extracellular factors. Defects in the synthesis, regulation or identification of growth factors can lead to cancer. In a healthy organism, there is always a balance between cell division and normal cell death and also differentiation. In case of loss of balance, the cell will be cancerous in which there would not be any control on the cell cycle[1-2]. The exact cause is not yet clear, however, some factors are effective such as genetic mutations[3] and environmental factors such as stress[4] as well as radioactive materials[5], toxic and chemicals materials, alcohol[6], and drugs[7-8].

Extensive works have been done in the fight against cancer since a few decades ago and remarkable progress has been achieved in this field[9], however, cancer is still one of the biggest worldwide health problems and researchers are looking for ways to cure it[10]. The most precise instruments need to be used in cancer treatment because the tissues involved in the disease may be responsible for the vital actions. Therefore, scientists are looking for the most accurate, safe

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methods with minimal side effects during treatment[11]. In this article, the methods employed in cancer therapy will be studied and ultimately the best method introduced up to date, immunotherapy, will be discussed.

Performance of the immune system is against foreign agents. Immune system is adapted to defend the body against a variety of pathogens such as the virus that causes polio and flat worms that cause schistosomiasis[12]. Immune system is comprised of an extend range of specialized cells and molecules that are able to identify and eliminate the invader and alien agents, all of these factors work together in a dynamic network. Pathogen detection by the immune system leads to the initiation of an enforcement response that can destroy or neutralize the aggressive agents[13]. Several components of the immune system are able to modify the initial diagnostic to a variety of effective responses, which each of them is uniquely appropriate to eliminate a certain type of pathogens. There are two immune systems, innate and acquired, which work together to protect the body[14]. The innate immunity consists of cellular and molecular mechanisms that cause of the are organized prior to an infection to prevent or relieve it[15].

The second immune system is known as the acquired immunity, which is formed through the response to infection, and is adapted in order to detect, to eradicate and to remind the invading pathogens. The acquired immunity is contingent on the innate immunity and is developed several days after the initial infection. The acquired immunity provides an extend and secondary line defense leading to eradicating pathogens that have escaped from innate response or, despite the responses, have remained in the body[16]. The immune system can be employed to cure many diseases, which the pathogens causing disease can be eliminated in this case. The method is called immunotherapy, since the host immune system is used to eliminate the pathogens. This method is mostly used in cancer treatment[17]. The cancer cells induce some changes on the surface that can act as an antigenicity agent and stimulate the immune system. One of the characteristics of cancer cells is to produce peptides as tumor peptides, known as tumor antigens[18].

Discrimination of self from non self using peptides

Proteins displayed on the surface of cancer cells may include one or more peptides or epitopes that are recognized by T cells[19]. Immune system should recognize and destroy pathogens, beside identifying and not destroying natural host proteins. Searching the protein antigens in host is mediated by major histocompatibility complex (MHC). MHC proteins attach to the peptide fragments of digested proteins within the cell, move them back to the surface and present them to other cell. During infection, the viral proteins are digested and presented by MHC proteins[20]. Foreign peptide fragments presented by MHC are the immune system antigens and recognized as non-self. T cell receptors bind to the fragments and continue the subsequent stages of immune response. There are two classes of MHC proteins which differ in their distribution among cell types and in the source of digested proteins. Class I MHC is found on the surface of virtually all vertebrate cells. These complexes of peptides and class I MHC proteins are the recognition targets of the T-cell receptors of the T_c cells in the cellular immune system[21].

The general recognition pattern of immune system was initially described in 1974 by Rolf Zinkernagel and Peter C. Doherty. Class II MHC occurs on the surface of a few types of specialised cells that take up foreign antigen, including macrophages and B lymphocytes that recognize foreign antigens[22]. Class I MHCI-peptide complexes on the surface of infected cells were recognized as a foreign substance and Tc cells attach them through the T cell receptors with proper binding characteristics.

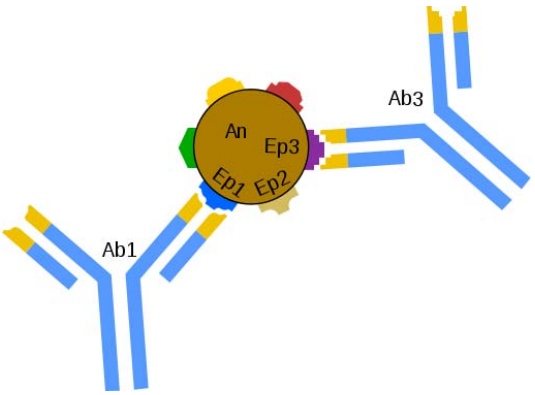

Fig. 1. A view of the antibody binding to the antigen, several epitopes may attach to an antigen due to different epitopes on its surface

T cell receptors only respond to the peptide antigens that form complexes with Class I MHCI proteins. T_c cells have another receptor called CD8 which is also called co-receptor and accelerates the binding interaction of the T cell receptors and MHC proteins[23].

T *cells* receptors on the T_H cells bind to the *peptides* that form complex with class II MHC proteins and are displayed on macrophages and B lymphocytes surfaces. T_H cells have also a co-receptor called CD4, which accelerates the interaction between the T cell receptors[24].

Types of cancer therapy

Surgery

Treatment by surgery is one the good treatment methods in which the cancer tissue is removed and the cancer spreading toward adjacent tissues is prevented. Several techniques are used in tumor surgery including Infusion, Perfusion, Chemosurgery, Cryotherapy, Cautery, and Laser [25]. In the first stages of many tumors, the surgical treatment is definitive and some of them can be cured by radiotherapy or both radiotherapy and chemotherapy can be applied to destroy the remnants of the tumor. Cancer in different parts can be treated with surgery. Cancer can be cured in different stages using surgery including breast, lung, lower esophagus, stomach, small intestine, colon, rectum, pancreas, ovary, endometrium, cervix of the uterus (in stage 0 "in situ" and stage1 I). Vulva, vulva, vagina, kidney, bladder, prostate, skin, eyes, salivary glands, lips, tongue, larynx, thyroid, malignant melanoma, bone and braine sarcomas and soft tissue sarcomas[26].

Radiotherapy

In this method, ionizing radiation is used to kill the tumor cells. All cells in the body are sensitive to radiation, however, the tumor cells are more sensitive to radiation than others. Radiotherapy is employed in the treatment of localized tumors that are sensitive. However some localized tumors are treated the same with surgery and radiotherapy, the choice of treatment should be evaluated based on experience, availability, time, cost of treatment, the results from the operated part after the treatment, the age and the general condition of patients. Radiotherapy is applied for definitive treatment of sensitive cancers like cervical cancer[27]. Radiotherapy can cure some tumors permanently by surgery or be applied to reduce the size of tumors in those that are sensitive. Radiotherapy can also be helpful in relieving pain, preventing blockage, fracture or reduction of pressure inside brain. Radiotherapy is sometimes used for inoperable tumors to make them operable after the radiotherapy. In radiotherapy, reducing the adverse effects is one of the treatment priorities, like other methods, in which it is important to identify the tumor correctly. Nowadays, imaging has contributed greatly to the goal with advances in X-ray and computerized tomography scans and magnetic resonance with and without spectroscopy, sonography and electronic portal. Accuracy in the use of radiation decreases the adverse effects such as effect on salivary glands in the treatment of head and neck cancer[28]. In order to provide a more advanced treatment, the Radiotherapy should be used with chemotherapy[29].

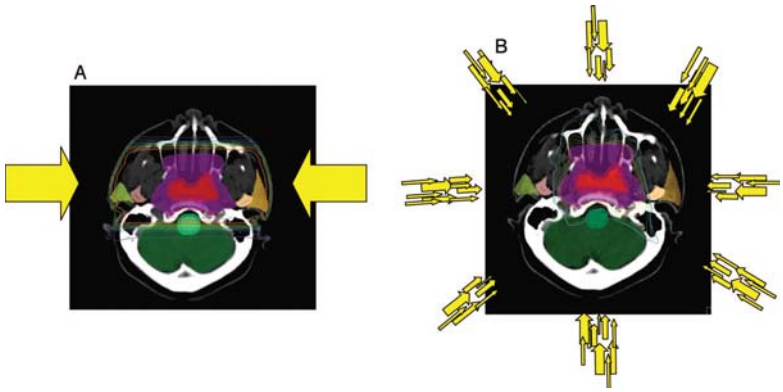

Fig. 2 (a) Two opposing beams of single intensities, represented by the yellow arrows, create a single-dose distribution through a nasopharynx tumor (GTV in red, CTV in purple) and normal tissue alike. **(b)** The beams from different angles to create the best image[28]

Chemotherapy

Advanced Chemotherapy was applied since the early 1940s, when the use of nitrogen mustard and anti-folate began. Since then, it was converted to a multi-billion dollar industry with strong support from the procedure[30]. It is used for advanced cancers or multiple metastases since it is the only means by which cancer cells in all over the body can be destroyed. Chemotherapy is able to improve some types of cancer completely and its ultimate influence is when the tumor is small. Chemotherapy can cause some side effects such as a decrease in the number of red blood cells, hair loss and also affect on healthy cells[31].

Immunotherapy

Brent McFarlane introduced the concept of immune surveillance in 1950, which is the physiological function of immune system, and means to identify and to destroy transformed cells prior to becoming tumor cells. It is now clear that innate and adaptive immunity systems act against many tumors and destroy them[32]. Tumor cells express some antigens which can be identified by the host immune system. The tumor-associated antigens (TAAs), displayed on the surface of cancer cells, are a factor to stimulate the immune system that following the induction of responsible immune system, may deplete the growth of cancer in various organs[33-35]. This process can be used to develop vaccines. Since a part of a molecule, as a foreign agent, can be recognized by host antibodies, it leads to a body's immunological response to foreign agents. Cancer cells also display some peptides on the surface, which differ from the normal host cells. It can be used to distinguish the cancer cells from the normal cells. This property is considerably helpful in both diagnosis and treatment[36-37].

Immune system stimulation to treat cancer

Immunological treatment of cancer attracts a great deal of attention to immunologists and cancer specialists. Since the current cancer treatments involve some drugs that kill or inhibit normal dividing cells in addition to cancer cells[38]. Therefore, many patients undergoing the cancer treatment may die[39] . While the immune responses specifically act against tumor antigens and the normal cells are not affected. Therefore, immunotherapy is considered as the most specific methods in cancer treatment. The tumor immunotherapy is aimed to actively strengthen the host's immune response against the tumor[40], or to provide an active immunity by the injection of antibody and tumor specific T cells. Nonspecific stimulation of the immune system to start an anti-tumor immune response have been common since several years before[41]. In new method, the vaccines containing antigens, killed tumor cells or dendritic cells treated with tumor antigens are used to develop an anti-tumor immunity[42]. Therapeutic approach of using tumor antigens includes passive and active immunotherapy. The passive immunotherapy is actually using antibodies against specific targets on the surface of tumor cells, such as monoclonal antibodies rituximab (anti-CD20), or transferring the tumor-reactive lymphocytes. In active immunotherapy, the immunity system is induced to response the tumor antigens (and therefore anti-tumor). From this category, the vaccines can be pointed including tumor cells, tumor cell lysate, peptides, carbohydrates, gene structures encoding protein, or antibodies against anti anti-idotopes antibodies which mimic tumor antigens. The active specific immunotherapy only activates one aspect of the immune system (such as B-cell or cell-T) that involve immediate anti-tumor effects and also memory responses to eliminate the activate tumor cells[43-44]. Most approaches in immunotherapy of malignancy are focused on the induction of CD8 T lymphocytes responses against the tumor antigens because these cells can be very effective in destroying tumor[45]. Thus, the researchers first began to identify peptide epitopes that stimulate the induction of CTL responses. Using the peptide epitopes leads to the induction of a strong CTL response in 91% of patients receiving the vaccine, but contrary to expectations, remarkable clinical responses were rarely observed, which is probably due to involving the CTL response alone[46]. There are abundant evidences regarding the importance of immune memory creation against tumor cells by TCD4[47]. TCD4 cells play an important role through interaction with antigen presenting cells in the early stages of CD8 T-cell activation and more stimulation of the cells[46, 48].

TCD8 cell function is improved through adding epitopes displayed with Class II MHC in peptide based vaccines[49]. Critical role of TCD4 cells is approved in controlling tumor growth and

protecting mice against class II MHC negative tumors. It was shown in a study that the transformation of the TCD4 cell-specific adapter of tumor induced virus FBL-3 (MuLV) can control tumor growth in an independent pathway of CTL[46] .On the other hand, the TCD4 cells have also lethal activity to assist host defense against tumors[50]. These cells also secrete cytokines to activate the executive cells of innate immune such as macrophages and NK cells[51]. But the major role of TCD4 cells is the induction of memory response in CTLs so that inhibits the tumor recurrence[47]. TCD4 cells cause the growth control and the persistence of antigen-specific TCD8 cells in the body, which is performed through the secretion of essential cytokines such as IL-2 in the adjacent to TCD8 cells[46]. TCD8 cells alone cause an short-term antigen-specific cytotoxic response without memory cells[52]. Hence, to make a long-term complete response against the tumor and eventually a complete destruction of tumor cells, the participation of both tumor specific CD4 and CD8 T-cells are required[53].

Production of anti-tumor vaccines

The immune system is very important in both cancer diagnosis and treatment. This property is highly effective in immunotherapy method or vaccine development against cancer. Immunity based immunotherapy seems ideal as a cancer treatment method, on the other hand, the cancer vaccine production will provide a significant progress in this field[54]. Today, many diseases have been eradicated with advances in vaccine development, since vaccines do not destroy the immune system. As viruses and other infectious agents disable the immunity system to improve infection, the vaccine stimulates the immune system due to the structural similarity to infectious agents or whatever is known as a foreign agent. Today, the vaccines with only an epitope that is considered as a stimulating agent in the structure are most used and the attenuated or even the killed vaccines are less used, because a probable mistake in attenuating or killing the infectious agent may lead to an infection or even dangerous consequences for an individual who has attempted to immunize for prevention [55-56]. Cells with an uncontrolled cell cycle, which cause a cancerous tissue, display some proteins on cell surface which differs from proteins on normal cells. This difference lead to the stimulation of immunity system[57]. This property can be used to make the vaccines to put the body in a standby mode, and then if the cell structure starts to change, the body reacts quickly to prevent the continuation and the improvement of process[58].

Immunization of individuals with cancer using the antigens displayed on the cell surface improves anti-tumor immune response. In designing different vaccine types, it is helpful to recognize the peptides of tumor-specific T cells and the ability of the cloning of genes encoding the tumor antigens recognizable by T cell lymphocytes[59]. Among the methods that can help the vaccine design is the injection of purified tumor antigens[60].

Recently, the therapeutic vaccines of dendritic cells are employed to immunize cancer patients against their tumor. In this method, to immunized the patients, the dendritic cells are purified from the patients and kept in adjacency to tumor antigens or transformed by genes encoding the antigens[61-63], then are reinjected back into the patient[64]. For example, a cell-based vaccine is designed to treat advanced prostate cancer. This vaccine is formed from the patient's peripheral blood cells enriched for dendritic cells. These cells are exposed to recombinant proteins containing colony-stimulating factor, granulocyte - macrophage (GM-CSF) and tumor associated antigen known as acid phosphatase prostate[65-66]. Another method in the vaccine design is using DNA that uses a viral plasmid encoding the tumor antigens[67-68]. Using the cell-based or the DNA-based vaccines are the best way to induce cytolytic T lymphocytes response.

Immunogenicity assay is not practical In the case of tumor-specific antigens, for example, those caused by random point mutations in normal genes, since the immunity system is specialized to identify a single tumor antigen. On contrary, those antigens that are common in many tumors like MAGE antigens[69], tyrosinase antigens[70], the melanoma antigens gp100[71], mutated Ras proteins antigens[72] and p53 antigens in many tumors[73], would be appropriate immunizers for certain types of cancer[74].

Virus-induced tumors can be prevented by vaccination with viral antigens or attenuated live virus. Like HPV vaccine vaccines which

reduces the incidence of HPV-induced tumors, including carcinomas of the cervix[75-77].

The role of epitopes in vaccine design

Epitopes are a part of an antigen that stimulates the immune response. Studying the epitope structure precisely will greatly be helpful in the vaccines design. Many studies have been performed to identify TCD4 cell-stimulating peptide epitopes to induce T helper response. After identifying the antigenic peptides that are able to induce T helper responses and cytokine production, TCD4 cells' potential to identify a complete protein form was evaluated. It was found that the generated colonies could identify the relevant antigenic peptides as well as the complete protein. The potential of TCD4 generated colonies was subsequently evaluated in identifying the normal processed forms of protein by the tumor cells, therefore, the tumor cells used in this study were manipulated to express class II MHC on the surface. The results showed the ability of TCD4 colonies in reidentifying the antigenic peptides that were naturally processed by tumor cells and presented with class II MHC[46, 50, 52-53, 78-80].

T helper response inducing Vaccine

After identifying the antigenic peptides bound to class II MHC, researchers were seeking to design vaccines to induce T helper response by using these peptides. A suggestive view in designing such vaccines was the use of tumor cells that can act as cell antigen provider.

But tumor cells normally reduce to the expression of class I and II MHC to evade the immune system and prevent the T helper response by several methods. Therefore, the researchers used a plasmid or vector containing the CIITA gene to induce the expression of class II MHC on the surface of tumor cells. The Ii-RGC gene enables the tumor cells to express the antigens through the endogenous pathway by class II MHC [81]. The tumor cells can be pulsed with antigenic peptides of the previous phase to cause the induction of T helper response. The use of these vaccine was largely successful in the induction of T helper response and subsequently in the further enhancing of CTL responses, however was unable to complete the tumor eradication [82]. The failure may be due to the lack of the expression of co-stimulatory molecules on the surface of tumor cells. The absence of co-stimulatory molecules in the tumor cells may lead to the anregy or the deletion of executive T cells, which is due to the lack of second signal by the molecules [83]. Hence, the T helper responses caused by vaccines are not as successful as the T helper responses induced by antigen-presenting cells, therefore, do not lead to a complete tumor eradication. There are some evidences that suggest the expression of Fas-L in some tumors such as melanoma which send the death message to activated T cells in the tumor [43, 83]. So in many vaccines, antigen-presenting cells (APC) or PBMC are used rather than the tumor cells both to present the recognized antigenic peptides near class II MHC and to provide the necessary stimulators to stimulate the T helper response. Many studies have proved that if the individuals' PBMC to become adjacent to the tumor antigenic peptides limited to class II MHC, T helper cells will be activated in the set and secretes cytokines like interferon-gamma, GM-CSF, TNF-α[78]. Mice models were firstly used to evaluate the help of activated TCD4 cells to CTL responses. The antigenic peptides limited to class II MHC were used in the vaccines containing the peptides limited to class I MHC. After administration to animals, the assistant effect of the induced T helper cell responses to CD8 activated T-cells by class I MHC peptides was clearly identified. These vaccine were more effective in stimulating immune responses against the tumor and creating memories[80].

Another major point in the success of a tumor vaccine against the T-cell activation is the role of MHC I/II types in tumor cells and antigen-presenting cells. As was mentioned, the simultaneous stimulation of CD8 and CD4 T-cells could be effective in the vaccine effectiveness. Therefore, the use of an elongated peptide containing several immunogenic epitope can guarantee the interaction of peptide with multiple alleles of the class I and II MHC and lead to the induction of a broad T-cell responses against many epitopes, and hence reduces the mechanisms which enable the tumor to escape from the immune system[44].

Limited studies are performed in terms of the induction of T helper response and its effectiveness in CTL response. In one case, investigators found that patients with an in vitro T helper response against antigenic peptides have

better clinical signs and greater percentage of complete tumor relapses compared to people who do not provide the response[50]. However, the method of vaccination for cancer patients is performed. The anti-cancer vaccines development is aimed to activate the host immune system to destroy cancer cells with a minimal toxicity to normal tissues as well. In recent years, the views of immunity to cancer therapy have been evolved from the treatment of patients with the non-specific stimulators of immunity system (such as bacillus calmette guerin for the treatment of bladder cancer) to the use of tumor antigens (TAA)[43].

Barriers to correct immune system response against tumors

Elimination of tumor cells by the immune system sometimes faces some problems such as the origin of the tumor cells. Since the tumor cells are derived from the host's normal cells, they have many features in common[84]. Antigens displayed by the tumor cells on the surface are poor and will produce a weak immune response. In general, the tumors that introduce foreign antigens and various mutant self proteins are able to stimulate a stronger immune response[36]. Such tumors are generally generated with virus[85] or chemicals compounds. Tumors that occur spontaneously in the body develop a weak immune response. In fact, the phenomenon of developing immunity against tumors is different. Another major point in the anti-tumor immunity is the rapid growth and the spread of tumor cells which enable them to overcome the immune system[86]. Another point is the escape of tumor cells from the immune response with a variety of specialized mechanisms[87].

Tumor escape Mechanisms from the immune response

Cancer cells use multiple mechanisms to evade the immune response including:

1. Tumors remove the antigens that stimulate the immune responses. Rapidly growing tumors normally lose their antigens. Due to the abundant mitotic division, the tumor cells are genetically unstable and the antigen encoding genes undergone mutations[88]. So these antigens will be removed if not be essential for tumor growth.
2. Decrease in class 1 MHC expression is another problem in the immune response to tumor cells[89].
3. Distance of the tumor antigens from the immune system's access: The surface antigens of tumor are covered with glycocalyx molecules which remain them hidden from the host's immune system[90]. This fact is known as the antigen hiding[91].
4. The majority of tumor cells do not introduce the stimulatory helper molecules or class II

Table 1. Classification of the tumor-associated tumor antigens detected by T cells

Antigen	Subgroup	Tissue distriution	Mechanism of expression
Differentiation antigens	Specific tissue lineage(e.g, melanocytes)	Normal and neoplastic tissues	Normal differentiation
Tumor-restricted, shared	Encoded by germ line but not by somatic cell genes	Different tumors: Normal testis and placenta (eg, MAGE)	Demethylation
	Lineage-related	Melanomas (eg, TRP-2/INT-2, GnT-V	Alteration in splicing or transcription
	Virus-induced (eg, HPV, HBV, EBV)	Cervix, head and neck, anus, penis, and liver	Encoded by different gene Mutation, translocation
	Oncogene, Oncosuppressor or fussion proteins	Cancers: Burkitt's lymphoma Different tumors	
Tumor- restricted, Unique		Single tumor only	Protein mutation
ubiquitous		Many normal and neoplastic tissues	Normal

MAGE: Melanoma antigen; TRP-2/INT-2 = intron 2 antigen / tyrosinase-related protein 2; GnT-V= N acetyl transferase glucosamine V; HPV = human papillomavirus; HBV = hepatitis B; EBV Epstein Barr Virus[95].

MHC molecules, therefore, they will not induce strong responses from the executive T cell. The presence of co-stimulatory molecules is needed to start the T cell responses and the presence of class 2 MHC molecules are required to activate helper T cells[92].

5. The usage of some molecules by tumor cells to inhibit the immune response in this case is another problem. Empirical evidences indicate that the inhibition of T cell responses to some tumors is mediated by CTLA-4[93] and [94] PD-1 molecules.

DISCUSSION

Given that humans are exposed to many risk factors, they are considered as major clinical problems and allocated a large part of the cause of death to themselves[96]. Nowadays, several factors have increased the cancer risk including, the number of beams used in industry, increased stress, industrial foods, drugs, alcohol and etc. So, the researchers are looking for methods to reduce the suffering of humanity in this regard[97-98]. Today, many method are used in cancer therapy such as radiation therapy, surgery, chemotherapy, hormone therapy, combination therapies, laser therapy and immunotherapy[99-100]. However, future methods and mainly based on biology and molecular genetics will be far more effective[101]. Independent to the efficient use of each of the current methods, the treatment of internal cancer involves some minor side effects, moreover, the current false cancer diagnosis rate is about 8.11 percent. Although efforts are increasingly focused on the importance that anti-cancer treatments to be reliable, efficient, with selective effects on the tumor cells, without side effects, and most importantly should be able to return the patient to normal situation[102]. These efforts have had fairly successful results. Surgery is considered as an oldest and largest cancer treatment method. Surgical removal of a tumor is relatively quick and effective and includes the most relative treatments of cancer. Surgery can also provide the possibility of a complete removal of the tumor, since it is possible to observe a layer of normal cells surrounding the tumor cells by pathology. Surgical procedure, which is typically applicable in only about 18% of lung cancers, unfortunately, contains come serious deficiencies such as high rate of injury, the lack of guarantee for a complete removal of the tumor, not applicable for metastatic cancer[103]. Another method is chemotherapy. The chemotherapy (and radiotherapy) is focused on the damage to the DNA molecule. Chemotherapy has also side effects, such as effects on both normal cells and cancer cells and also the probability of being ignored by cancer cells[104]. Another technique that can be an optimized method for the treatment and the prevention of cancer is immunotherapy. It will be helpful if the immune system be placed in a standby mode to suppress the tumor. The cancer cells can exhibit certain surface antigens or change their cellular level, which can be a good candidate for stimulating the immune system to respond cancer cells. The use of such property of immune system can be an appropriate method in cancer therapy. Vaccine development base on the antigenic structures present on the surface of cancer cells, the change of cell shape or DNA, is an efficient method in preventing cancer. For example, a cell-based vaccine is designed to treat advanced prostate cancer. This vaccine is composed of the patient's peripheral blood cells enriched for dendritic cells, which are exposed to recombinant proteins including, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor associated antigen known as prostatic acid phosphatase. In this case, the body is placed in a standby mode, therefore, once the cells became cancerous, the immune system will recognize and react to it. Immunotherapy is an optimal method since the shocks and strikes used in the other methods are not needed in it. However, the cancer cells can avoid stimulating an immune response in different ways, for example by changing or lacking the expression of specific antigens, which can be problematic in the vaccines development. To solve this problem, first the carcinogenesis pathways must be properly identified, as well as the mechanisms by which these cells trick the immune system. Since then, the tumor formation can be prevented and treated with minimal impacts and safest methods. Consequently, the cost of treatment and adverse clinical problems found in the other methods will be decreased as well as the stress exerted on the patients and their relatives.

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