Treating Cancer with Vaccine

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The therapeutic vaccines are supposed to induce the patient’s own immune system to specifically recognize and eliminate tumor cells. TSAs, which are present only on tumor cells, and TAAs, which are present mostly on tumor cells but also on some normal cells, can be the potential target of the immune response. It has been shown that several proteins, classified as TSAs, are essential for tumor genesis and cancer progression. That is why TSAs could be a perfect target for cancer vaccines. On the contrary mutations are mostly tumor-specific and unique, thus developing personalized immunotherapy for each individual patient could be required. On the other hand TAAs are not specific and can be found on tumors with the same histology as well as on tumors of different origin. In contrary to TSAs, TAAs trigger only a weak immunological response due to self-antigen tolerance (1).

Adjuvants or biological modifiers improve vaccines by increasing the magnitude of the response (3). They can activate antigen-presenting cells (APCs), natural killer cells or other cells of the innate immune system. While APCs stimulate a potent and robust cellular immune response (T cells), the other two activated cell types produce cytokines, which can promote survival of antigen-specific T cells (5). For now, only a few adjuvants, such as aluminium-based salts (alum) and a squalene–oil–water emulsion (MF56) are licensed for human use (6).

When designing a vaccine it is of great importance to choose the proper antigen and the suitable adjuvant to get the desired immune response. To ensure that the immune response, generated by the vaccine, destroys only the antigen-bearing tumor cells, without damaging normal cells, the antigens should be molecules that are present only on tumor cells and cannot be found on normal, healthy cells. The desired immune response, in the case of a therapeutic vaccine, should ensure not only the eradication of tumor cells, but also prevent a recurrence of the disease. In the case of a prophylactic vaccine it should also prevent new tumor
The immune response should provide a life-long protection from cancer, therefore it must result in long-term immune-cell memory (5,7). The lack of TSAs and the weakness of the immune response against TAAs are one of the biggest problems in developing efficient cancer vaccines. The immune system usually recognizes the TAAs as self-antigens and does not respond. Therefore there have been various strategies proposed to overcome this weakness, such as cell-based, DNA-based, RNA-based, protein-based, peptide-based and vector-based vaccines, with the purpose to activate the APCs and stimulate the antigen-specific cytotoxic T lymphocytes (CTL) mediated immune response. The most potent APCs are the dendritic cells (DCs), which have shown the best results in activating T cells (1). In the last decades many mechanisms were developed to induce the DCs, which in turn activate the T-helper cells (Th) and CTL response against tumor antigens and bypass the immune tolerance to self-antigens. These are the following mechanisms: (a) infecting DCs with viral, bacterial, or yeast vectors, (b) pulsing DCs with proteins or peptides, (c) loading DCs with tumor cells or tumor-cell lysates, and (d) transfecting DCs with DNA or RNA (1,5).

The latest studies are researching the possibility to increase vaccine-induced immunity by the combination of vaccines with low doses of chemotherapeutic agents, such as cyclophosphamide, doxorubicin and docetaxel, or radiation therapy (1).

**Vaccines based on bacterial or yeast vectors**

Many vectors exist that can be used to transport recombinant genes (including genes expressing TAAs, co-stimulatory molecules, or cytokines) into APCs. In cancer immunotherapy mainly bacterial, yeast or virus vectors are used. Vaccines with recombinant vectors can induce the immune system to provide a strong inflammatory response, which is directed mainly towards vector proteins. These could increase the immune response against the genes that have been inserted into the vector. This type of transport of recombinant proteins is much more immunogenic than administering the protein with adjuvants (1).

Each vector has its own characteristics and can stimulate the immune system in its unique way, which is why the choice of a vector is important. There are also other factors that should be considered before the production of such vaccines: (a) the balance between the stimulation of innate versus adaptive responses; (b) the balance between the stimulation of Th1 versus Th2 responses; and (c) the preferred activation of subsets of cells mainly committed to regulatory (Tregs, Tr1, and Th3) or proinflammatory functions (Th17) (1).

Bacterial vector vaccines are highly immunogenic, but their clinical application is limited with safety concerns, pre-existing immunity and inhibited repeat immunization. Bacterial carriers that deliver either plasmids or proteins to APCs are for example L. monocytogenes, Salmonella spp., Shigella spp. and Escherichia coli. For instance studies have shown that Listeria monocytogenes could lead to regression of pre-existing E7-expressing murine tumors. Attenuated Salmonella and Bacille Calmette-Guerin (Mycobacterium bovis) on the other hand have been used to develop vaccines encoding HPV-16 L1 and E7. They can induce E7-specific antibody and cytotoxic immune responses (8).

Saccharomyces cerevisiae is an example of a yeast vector that contains the transgene encoding carcinoembryonic antigen (CEA). Vaccines with this vector are capable of activating human DCs and stimulate CEA-specific T cell responses (9).

**Vaccines based on recombinant viruses**

Viral infections create the danger signal, which is necessary for immune activation and results in inflammatory reactions. This intrinsic ability to initiate immune responses is a huge advantage for vaccine with virus vectors (10). An ideal virus vector vaccine should be safe for clinical use, which means that it should not be able to replicate in patients’ cells. It should also be effective in inducing long-term antibody and T cell response (5). Human clinical trials have been initiated, based on recombinant viruses, which have been used in animal tumor models first. These recombinant viruses are for instance vaccinia-viruses, herpes simplex viruses, adenoviruses, adeno-associated viruses, retroviruses and avipox viruses (10). Vaccine based on recombinant viruses was also administered together with chemotherapy, but there is not enough sound evidence to support such treatment (5).

Vaccinia-virus is a poxvirus and was the first virus that was used as a vector over 20 years ago (5). The large amounts of foreign DNA that can be inserted into vaccinia-viruses still makes them a very attractive vector to use nowadays. It also has a wide host and cell range, stable recombinants, a replication that is accurate, efficient post-translational processing of inserted genes and expressed recombinant proteins that are more immunogenic. Vaccinia virus has been
administered to over one billion people in the smallpox eradication program, which is another advantage, since this vector has been proven safe to use. On the other hand the vaccinia-virus proteins are highly immunogenic and could be administered maximally two times, since the following doses would be neutralized by the immune system. Another concern is the patient’s immune system, which would have to be immunologically competent, since vaccinia-virus could replicate after being administered (11).

PSA-TRICOM (also known as PROSTVAC) is a vaccine consisting of recombinant vaccinia-virus encoding prostate specific antigen (PSA) and recombinant vaccinia-virus encoding three co-stimulatory molecule transgenes B7.1, ICAM-1, and LFA-3 (TRICOM). In a phase II clinical trial 122 patients with metastatic hormone-refractory prostate cancer (mHRPC) were divided in a 2:1 ratio. PSA-TRICOM received 82 patients; the other 40 were treated with empty vector placebo. It was reported that the vaccinated patients had a greater 3-year overall survival (OS) and an improvement in median OS of 8.5 months (1).

Vaccines based on proteins or peptides

Another type of potential cancer vaccine is based on proteins or peptides. The effectiveness of such vaccination relies on the in vivo ability of loading empty MHC molecules on professional APC that express co-stimulatory molecules. In order to successfully induce a polyclonal T-cell response, a peptide-based vaccine should contain several T-cell epitopes to cover a wide range of different MHC types (10). Production, storage and distribution of these vaccines are faster and more cost-effective. Another advantage is also the fact that the identification and administration of TSAs is preferable since tumor-cell preparations mostly contain self-proteins with no therapeutic benefit. On the other hand these vaccines are potentially capable of generating an autoimmune response. Their use is HLA restricted and limited to a subset of patients (usually HLA-A2+). Other disadvantages are also the weak immunogenicity of a single protein and a poor ability to induce balanced activation of CD4- and CD8-receptor (1).

Peptide-based vaccines are safe and their production is easy, but we have to overcome their weak immunogenic properties and the need for HLA matching. Protein-based vaccines on the other hand are less depended on the patient’s HLA types (8). Sipuleucel-T (an investigational immunotherapy product) stimulates T-cell immunity to prostatic acid phosphatase. Prostatic acid phosphatase (PAP) is an antigen, which is expressed only in the majority of prostate cancers. A fusion protein termed PA2024 is cultured with APCs in Sipuleucel-T and consists of PAP linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). It provides efficient loading and processing of antigens by APCs. This product’s safety and efficiency was evaluated with randomized, placebo-controlled phase III clinical trial of 127 patients with metastatic, asymptomatic hormone refractory prostate cancer, which were divided in a 2:1 ratio. The patients received three infusions of Sipuleucel-T or placebo every two weeks. The analyses demonstrated that the patients treated with Sipuleucel-T lived 4.5 months longer. The median for time to disease progression for Sipuleucel-T was 11.7 weeks compared with 10.0 weeks for placebo (12).

Stimuvax is a liposome vaccine that induces immune response against peptide MUC1, which is a type I membrane glycoprotein that is expressed on many tumors (lung, breast, prostate and colorectal cancer). Randomized phase IIB study evaluated survival and toxicity of 171 patients with non-small-cell lung cancer; 88 of them received infusions of Stimuvax, the other 83 received best supported care. Median survival time of 17.4 months was achieved by patients that received Stimovax, while the other patients achieved a median survival time of 13 month. Patients that were assigned to the Stimuvax lived 4.4 months longer and no toxic side effects were observed (13).

Vaccines based on tumor cells or their lysates

Tumor cell-based vaccines consist either of autologous (patient-specific) or allogeneic (non-patient specific) tumor cells, which can be unmodified or modified for expression of MHC and can also be used as tumor-cell lysates (1). Cytokine genes or co-stimulatory molecules are induced into the genome of the vaccine tumor cells, because original tumor cells itself cannot induce an adequate immunological response. The granulocyte-macrophage colony-stimulating factor (GM-CSF) is an important cytokine that contributes to the maturation of DCs. Mature DCs on the other hand enhance the presentation of antigens in vivo. The production of these vaccines is rather slow, difficult and labor-intensive (10). OncoVAX is an example of these vaccines, which is composed of autologous irradiated tumor cells. A
Randomly chosen 254 patients with stage II and III colon cancer were divided into two groups. One served as a control group and the other was treated with OncoVAX. After 5.8 years, a 20.4% reduction in risk of disease progression in patients receiving OncoVAX was reported. In stage III disease no significant improvement were observed. In stage II on the other hand were improvements with a 41.4% reduction in relative risk of disease progression in patients receiving OncoVAX (1).

**DNA- and RNA-based vaccines**

DNA and RNA vaccines are easily, cheaply and conveniently to produce and do not require special handling or storage conditions. They elicit immune responses only to the encoded antigens and can be either directly administered to the host as a vaccine or be used to transfect DCs in vitro and use these tumor antigens producing DCs for the immunization (5). Nevertheless DNA vaccines have been developed recently, they have already been proven capable of activating a strong immunity response. They are used to deliver a bacterial plasmid to the host. A particular gene encoding a tumor antigen of interest is inserted into the bacterial plasmid and enables the host to synthesize the encoded tumor protein. This protein is transported into the lymph node where it can induce both humoral and T cell mediated immunity (5,10). The immunogenicity of these vaccines can be enhanced with improved delivery systems, simultaneous administration of cytokines, use of separate plasmids encoding nonself-antigens and various modification of plasmid-encoded antigens (1). One of the first clinical trials for a DNA vaccine was against HIV-1 virus, followed by trials against cancer, influence, malaria, hepatitis B and others. These trials proved the DNA vaccines to be well tolerated and safe to use (2).

Even more recent approaches are RNA-based vaccines that can avoid the integration of the DNA into the recipient’s genome, a problem that may arise with DNA-based vaccines and is associated with malignant cell transformation. On the other hand the efficacy of RNA-based vaccines could be compromised by degradation of the RNA molecule by the RNases enzymes in body fluids and skin (5). There have been also studies with mRNA-based vaccine, which contains the mRNA-coding TAA. Such vaccine is transfected into DCs and translated into proteins. Therefore the antigen can be loaded on MHC molecules for antigen presentation and an antigen-specific CTL response can be activated (1). In more recent studies, the use of naked RNA, which represents RNA that is transfected into DCs without the help of additives like liposomes or electroporation, has been analyzed, but only in a few vaccination trials. They have demonstrated that these vaccines could induce CD4+ and CD8+ T cell responses and are safe. Only mild and reversible side effects occurred during these studies, anyhow better clinical outcomes between study and control group were rarely observed. Therefore the latest studies deal with the enhancement of the effectiveness of vaccines. However, more trials might be needed before the best vaccination schemes will be found (14).

**Conclusion**

The goal of vaccine-based immunotherapy for cancer diseases is to challenge a sufficient potent immune response that cause elimination of tumor cells and provides a life-long protection from cancer. Therefore it must result in long-term immune cell memory. Currently there are many promising vaccines under investigation. For now, they still have to be clinical tested, proven effective and later successfully implemented into everyday clinical practice.

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