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CANCER VACCINES

It is well known that the main cause of low anti-tumor immune response lays in the low antigen difference between normal and tumor cells. New approaches to enhance the specific and non-specific immune reactions were intensively studied during the last years. The discovery of tumor-assosiated (TAA) antigens started the modern era of oncoimmunology. The structure and/or expression level of these antigens was shown to be different from those of normal cells. Ineffective immune response of cancer patients could be explained by the low immunogenicity of TAA, the synthesis of immunosuppressive molecules, local expression of inhibitory molecules, disruption of lymphocyte regulatory functions, inability to present antigen, and weak contact with tumor surface antigens. Some TAA were identified, but yet it is not clear, which of them could be targeted in clinical setting. The research in oncoimmunology should help to develop the approaches to enhance TAA immunogenicity.

There are two main immunotherapeutic strategies. The first one is the injection of antibodies or mature T cells that could attack malignant cells to the bloodstream of cancer patients, and this could be called "passive immunotherapy". The second strategy is based on cancer vaccines (CV), which are directed against immunogenic antigen and stimulate the anti-tumor immune response. The last strategy is regarded as very perspective. There are two groups of CV — preventive and curative.

Preventive vaccines applied to prevent tumor growth in healthy people from so-called "risk groups". These CV induce specific immune response against oncogenic virus proteins. Two preventive CV against hepatitis viruses B and C, which could promote hepatocarcinoma, are undergoing the initial phases of clinical trials. The only vaccine of this type, which already underwent clinical trials and is allowed for clinical use, is the vaccine against human papilloma virus (HPV). HPV16 and 18 were shown to be strongly associated with cervical cancer (70% of cases), whereas types 6 and 11 were found in 90% of condylomas. The licensed vaccine contains the proteins of these four types of HPV and is DNA-free. Preliminary clinical trials have demonstrated the safety and tolerance and also high immunogenicity of this vaccine. The prevention by vaccination of condyloma and pre-cancer states of cervix and vagina was shown to be quite effective.

Curative cancer vaccines are generally prepared form cancer cells, which serve as an antigen source. In some cases, these vaccines could be based on recombinant tumor-specific or tumor-associated proteins. The essential feature of curative vaccines is that they could not be used for cancer prevention because of wide diversity of tumor types and impossibility to guess the individual specific proteomics of tumors. But curative vaccines definitely could be used for treatment of patients with known cancer types and for prevention of recurrence and metastasis.

The design of curative CV starts from the determination of perspective immune system targets (tumor antigens). More than one hundred antigens were proposed as potential candidates for CV, and their number is growing very fast. When the antigens are chosen, their immunogenicity should be improved by adjuvants that enhance immune response to foreign antigens. The spectrum of adjuvants is very broad — from simple small molecules, called haptens, to modified living cells.

What are the strategies used to increase the immunogenicity and the efficacy of CV? One way is to vaccinate by recombinant viruses expressing TAA. Another approach is the creation of genetically modified vaccines. For this purpose autologous or allogeneic tumor cells are transformed by vector DNA, which results in expression of specified proteins, for example, cytokines that activate immune response.

There are few types of curative CV, which are now under development:

Whole cell vaccines prepared from patients tumor cells (autologous vaccines) or from cell lines with known spectrum of tumor antigens (allogeneic vaccines). Cells are killed by lyzis or irradiation. These vaccines usually introduced together with adjuvants — BCG vaccine, lipopolysaccharides, Freund's adjuvant, etc.

Antigen-adjuvant CV composed from specific protein fragments or peptides. Peptide antigens potentially are more effective than whole proteins. Moreover, peptides could be more easily obtained in big quantities.

Dendritic cells that were taken from patients, then stimulated by tumor antigens and re-injected to the patient. This CV activates T lymphocytes, which quickly proliferate and attack tumor cells, which express specific antigens.

DNA vaccines that code tumor-associated antigen. Usually it is a vector (plasmid, recombinant virus), which effectively transform cells and contain promoter for specific antigen expression. Such construct could code few antigens at once.

Anti-idiotype CV represents antibodies against anti-TAA antibodies, which could activate immune response with the same effectiveness as TAA-containing vaccines.

To speed up the process of clinical trials and introduction of cancer vaccines to clinics, joint intensive research should be performed by scientists and clinicians. There is still a lot of work that should be done, but finally it will give an additional tool for oncologists to make cancer treatment more effective.

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