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# IMMUNOTHERAPHY OF CANCER

***Summary.*** *The article dedicated immunotherapeutic approaches in treatment of cancer, including: direct administration of auto- and allogenic anti-tumor vaccines, employment of dendritic cells pulsed with specific tumor associated antigens, use of viral vectors for delivery of genes encoding for chimeric antigen receptors to T-cells, application of cytokines able to activate T-cells against tumor, and introduction of checkpoint inhibitors able to deduce T-cells anergy.*

***Key words:*** *immunotherapy, vaccines, tumor associated antigens, T-cells, dendritic cells, chimeric antigen receptors, cytokines, checkpoint inhibitors.*

A unique feature of immune system is its ability to protect human body not only from infectious agents but also from cancer cells.

The first idea of a possible protective antitumor function of the immune system was expressed by Virchow in 1863, when he showed an immune infiltrate in tumor. Then Coley tried to use products, isolated from a mixture of killed bacteria of the *Streptococcus Pyogenes* and *Serratia Marcescens* species, as an antibacterial agent for patients suffering from malignant neoplasms.

In 1909, Erlich hypothesized that nascent mutated cells constantly appear in our bodies but the immune system constantly gets rid of them even before the onset of clinical symptoms. In the mid-20th century, it was shown that the growth of a transplanted tumor can be suppressed by the immune system. The results of these studies have convincingly shown the existence of tumor-associated antigens (TAA) and the presence of an immune surveillance system in the body. The inhibitory effect of Bacillus of Calmette and Guerin (BCG) on the growth of recurrent bladder cancer, which has even received clinical use, has also been discovered [1].

The immune response against cancer cells can be divided into three phases: 1) an innate immune response; 2) activation of specific T cells against cancer; and 3) destruction of tumor cells by T killer lymphocytes.

If oncogenic transformations are detected in the first scenario, the defective cells are usually removed by granulocytes, macrophages or Natural-Killers (NK) lymphocytes. During this phase, some of the tumor antigens are internalized by dendritic cells (DC) and their fragments presented by the major histocompatibility complex class II (MHC-II) to the effector cells. This step normally takes place in the lymph nodes, where DC transmit information about the oncogenic antigen to the effector naive T-lymphocytes [2].

Interaction between DC and naive T cells leads to the formation of a class of specific T cells, cytotoxic CD8+ T lymphocytes, which are able to recognize exposed tumor antigens on the surface of cancer cells and destroy them.

The last phase is the migration of CD8+ T lymphocytes to the tumor location site following the attack of tumor cells. CD8+ T-cells are able to kill tumor cell by two mechanisms: 1) either through the production of perforine and granzymes or 2) FAS-FAS-ligand interaction. Upon entrance granzymes into the cytoplasm of the target cell their serine protease triggers the caspase cascade, which is a series of cysteine proteases that subsequently lead to apoptosis. Alternatively, CD8+ T-cells are able to express the surface protein FAS-ligand, which can bind to FAS molecules (CD95L or Apo1L) expressed on the target cell. The FAS-associated death domain, so-called, FADD translocates in the cell, allowing recruitment of both procaspases 8 and 10, which lead to an alternative way conducing cells to apoptosis. Although FAS is the dominant death receptor pathway utilized by cytotoxic T lymphocytes, cytotoxic signaling via TNF receptor 1 (TNFR1) and TRAIL receptor (TRAILR) also converge on FADD and caspase-8 activity and lead to apoptosis [3].

The main immunological approaches in fighting cancer are summarized into five categories: 1) direct administration of immunogenic tumor antigens; 2) use of DC pulsed with specific tumor antigens; 3) application of specific T-cells loaded with immunogenic tumor antigens; 4) employing cytokines able to activate T-cells against tumor cells; 5) modifying the microenvironment by inhibiting stimuli able to induce T-cells anergy.

Several attempts have been made to develop antitumoral vaccines, which can be classified into three main categories, such as: 1) cell vaccines (tumor or immune cell); 2) protein/peptide vaccines; and 3) genetic (DNA, RNA, and viral) vaccines. Despite considerable efforts in developing cancer vaccines, only a few of them have reached clinical approval and medical practice.

Autologous tumor vaccines prepared using patient derived tumor cells represent one of the first types of cancer vaccines tested. Tumor cells, which harvested from the tumor site, irradiated, combined with immunostimulatory adjuvant molecules, for example, BCG or alum and re-inoculated in patients. Last generation of autologous vaccine able to express IL-12, a key cytokine that promote helper Th1 immunity, showed also strong tumor suppression accompanied by high IFN-γ production and increased activation of cytotoxic T lymphocyte (CTL) and natural killer (NK) cells [4].

Allogeneic whole tumor cell vaccines, which typically contain two or three established human tumor cell lines, mainly used with the purpose to overcome many limitations of autologous tumor cell vaccines, such as the difficulty to obtain a large number of immunogenic cancer cells from the tumor site and associated cost.

According to the second abovementioned approach dendritic cells can be employed to synthesize anti-tumor vaccines as an alternative to cancer cells, DCs are the most potent antigen-presenting cells (APC), which in the peripheral tissues uptake, process and present host-derived antigenic peptides through the MHC type II to naive T lymphocytes in the lymphoid organs. Outside the body DC can be generated in culture made from peripheral blood-derived mononuclear cells (PBMC). Made by this way the final anti-cancer carriers pulsed with TAA and IL-2 and are administrated back in patients to induce anti-tumor immunity. Up today the only DC-based vaccine used in clinic is the Sipuleucel-T [5].

The main limitation of usage individualized whole tumor cells or DCs is the complex procedure of preparation autologous vaccines. To a certain extent, these limitations can be overcome by the introduction of peptide vaccines. Most peptide-based vaccines in clinical trials target certain oncofetal antigens (MUC-1, CEA), cancer-testis antigens or cell differentiation-associated antigens. Although these vaccines were able to induce antigen-specific T cell responses, clinical outcomes have been not so encouraging [6].

It should be emphasized that TAAs generally exhibit weak anti-cancer activity and require additional immunostimulatory adjuvants for generation effective immune response. Recently acquired data suggest that the activation of innate immunity is required to drive adaptive immune responses. Adaptive immune responses are preceded by, and dependent on, innate immunity receptors, which could be triggered by microbial components. The coordination of innate and adaptive immunity is assured by the so-called toll-like receptors (TLRs) on the surface of cytoplasmic membrane of dendritic cells, and activated by direct contact with conserved moieties either pathogen itself or pathogen-associated molecular patterns of infected cells. Activation of TLR is able to reinforce adaptive response against both pathogens and cancer cells. The use of attenuated pathogens with the ability to enhance their action toward the TLR has been proposed for anticancer immunotherapy. A classic example of exploring this approach is the Bacillus Calmette-Guerin (BCG) vaccine from attenuated strains of *Mycobacterium bovis*. Furthermore, this type of vaccine is the most used in the world. BCG administration after transurethral resection is the standard treatment for non-muscle invasive bladder cancer.

Another strategy to deliver TAA to the patients affected by cancer is the use of viral vectors. An oncolytic herpes simplex virus type 1 (HSV-1), encoding for granulocyte macrophage colony-stimulating factor (GM-CSF), named T-VEC (talimogene laherparepvec), has been employed for treating patients with advanced malignant melanoma and has demonstrated good efficacy [7].

Despite the considerable progress made in the field of anti-tumor vaccine therapy, currently only Sipuleucel-T, BCG, and T-VEC are used in clinical practice.

Recently, another and the most promising strategy for increasing specificity of T-lymphocytes against TAA has been developed and got its name as CAR technology. The CARs (chimeric antigen receptors) are chimeric transmembrane receptors constructed by fusion of an antigen specific single-chain variable fragment against TAA and CD3 intracellular domain of T-cell receptor (TCR). The standard procedure includes transfection of a viral vector, carrying a gene encoding for CAR, to the patient's autologous T-cells with the result of expression on the surface of T lymphocytes a highly specific receptor against its oncological TTA target. The

CARs can be divided into first, second and third generation depending on the presence in the chimeric gene of none, one or more co-stimulatory intramembrane domains of CD28, 4-1BB, and OX40 [8].

The idea of generating highly selective T-cells against oncological TAA prompt to the design of several clinical trials aimed to verify in the clinic the areas efficacy of CAR. To our regret, despite ongoing success in treatment of CD19+ B-cell hematologic malignancies, the analogous results have not been obtained in the solid tumors. The main cause of such failure is the difficulty to identify effective TAA, against which the immune attack should be directed [9].

Three-four decades ago, it has been observed that some solid tumors, such as renal cell carcinomas and melanoma, were more immunogenic than others were because they showed a positive regressive dynamics upon administration of high doses of cytokines and at the same time were resistant to the conventional chemotherapy. Interestingly, cytokine therapy provided robust benefit only in a subset of patients, who developed autoimmune reactions. Several cytokines have been employed in the clinical practice but only two of them, namely IL-2 and IFN have found clinical application. Attempts of direct administration of cytokine mixtures, known under a name of "multikine", leaded to the controversial results. Although initially cytokine IL-15 showed promising anti-cancer results, it use in clinic is limited by its short half-life *in vivo* [10].

Actions on the inhibitory microenvironment, in which the T-cells mature, represent another approach of controlling tumor growth. There are several inhibitory receptors on T-cell membrane (CTLA-4, PD-1, TIM-3, BTLA, VISTA, LAG-3), which can be targeted by so-called checkpoint inhibitors, such as CTLA-4 inhibitors and PD-1/PDL-1 inhibitors that act by deleting the microenvironment suppressive effect on T-cells, letting them wake up from anergy, be reactivated and carry out their anticancer function. Some of them already have been tested in clinical trials, but at the present, only ipilimumab has used in clinic for treatment advanced malignant melanoma [11].

Concluding this short review it should be noted that the immune system is able to protect humans not only from infectious pathogens, but also from cancer. Cancer, especially in later phases, is responsible for immunosuppressive activity against immunocompetent cells, producing an array of inhibitory molecules, effects, and mechanisms, including: cytokine TGF-beta, IL-10, prostaglandins (PGs), activation-induced T-cell death (AICD) mehanism, FAS counterattack, impaired expression of T-cell receptor ζ chain, disruption of activation of NFκB in T-cells, mechanisms of resistance of tumor cells to cytotoxicity, disruption of induction of apoptosis, expression of membrane complement regulatory proteins by tumor cells, evasion of immune reactivity by tumor cells, disruption of antigen processing and presentation by tumor cells, reduced expression of MHC class I determinants [12]. This list of interal cancer cell self-defense mechanisms can be seen as exellent targets for development of new anti-cancer drugs.

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***Г. Анбарсіоглу, В.А. Малиновський. Імунотерапія раку. – Стаття.***

***Анотація.*** *Стаття присвячена імунотерапевтичним підходам до лікування раку, в тому числі: прямому використанню ауто- і алогенних протипухлинних вакцин; застосуванню дендритних клітин зі специфічними пухлинними антигенами; використанню вірусних векторів для доставки генів, що кодують рецептори химерних антигенів, у Т-клітини; впливу цитокінів, здатних активувати Т-клітини проти пухлини; і впровадженню циклічних інгібіторів, здатних блокувати інгібування Т-клітин.*

***Ключові слова:*** *імунотерапія, вакцини, пухлинні антигени, Т-клітини, дендритні клітини, химерні антигенні рецептори, цитокіни, циклічні інгібітори.*

***Г. Анбарсиоглу, В.А. Малиновский. Иммунотерапия рака. – Статья.***

***Аннотация.*** *Статья посвящена иммунотерапевтическим подходам к лечению рака, в том числе: прямому использованию ауто- и аллогенных противоопухолевых вакцин; применению дендритных клеток со специфическими опухолевыми антигенами; использованию вирусных векторов для доставки генов, кодирующих рецепторы химерных антигенов, в Т-клетки; влиянию цитокинов, способных активировать Т-клетки против опухоли; и внедрению циклических ингибиторов, способных блокировать ингибирование Т-клеток.*

***Ключевые слова:*** *иммунотерапия, вакцины, опухолевые антигены, Т-клетки, дендритные клетки, химерные антигенные рецепторы, цитокины, циклические ингибиторы.*

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# КОСМЕТОЛОГИЯ И ЛЕЧЕБНАЯ КОСМЕТИКА

***Аннотация.*** *В статье приведен анализ литературных данных и практических работ по современной косметологии, лечебной косметике, нутрикосметике, улиткотерапии.*

***Ключевые слова:*** *состояние кожи, косметика, косметические препараты.*

Современная косметология решает вопросы исправления недостатков внешности человека. Для этого врачи-косметологи изучают причины, вызывающие различные нежелательные эффекты на коже, разрабатывают способы их устранения и коррекции.

Уход за кожей лица представляет собой непростую задачу, которую возможно разрешить, придерживаясь основных правил по уходу за кожей. Они одинаковы для всех, независимо от возраста и типа кожи. Индивидуально подбираются лишь сами косметические средства.

Производство косметики не требует проведения глубоких исследований и клинических испытаний. Качество косметики заключается в том, чтобы ее продукция не содержала различных микроорганизмов.