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The role of immunotherapy in cancer treatment

Rola immunoterapii w leczeniu chorób nowotworowych

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Abstract

Cancer is a genetic disease with the growth of tumor cells initiated and promoted by mutations in a group of genes known as drivers. This is just the beginning of the process of cancerogenesis, characterized by cellular, genetic and epigenetic alterations as well as the loss of normal cellular regulatory processes. The revelation of complexity of mechanisms underlying the Cancer-Immunity Cycle has resulted in defining immunological and histological profiles responsible for suppressing or promoting anticancer immunity. It has been observed that such profile is determined not only by intrinsic tumor properties, patients' genetics, but also such extrinsic elements as gut microbiota, the presence of infection or exposure to sunlight. The balance between these factors, known as a cancer-immune set point, is a threshold that must be exceeded for a patient to respond to immunotherapy. Among various types of cancer immunotherapy, we can distinguish an adoptive T cell transfer, checkpoint blockade and neoantigen vaccines. The genuine features of human immune system, such as specific recognition and elimination of cancer cells, adaptation to an evolving tumor and immunological memory seem to be a perfect combination to create a powerful weapon for long-term cancer control. Nevertheless, the exact understanding of immunological mechanisms in both tumor growth and cancer elimination requires more thorough studies and may lead to enhancing the efficiency of a wide variety of immunotherapeutic anticancer approaches.

Keywords: immune system, immunotherapy, neoplasms

Streszczenie

Nowotwory należą do chorób genetycznych, wynikających z nadmiernego namnażania komórek zainicjowanego i promowanego przez różne mutacje. Jest to jedynie początek całego procesu kancerogenezy charakteryzującego się zmianami na etapie komórkowym, genetycznym i epigenetycznym, jak również upośledzeniem wielu funkcji regulatorowych. Złożoność mechanizmów odpowiedzialnych za interakcje między układem odpornościowym a procesem nowotworzenia przyczyniła się do zdefiniowania profili immunologicznych i histologicznych odpowiedzialnych za hamowanie lub zwiększanie odporności przeciwnowotworowej. Zaobserwowano liczne zależności ukształtowane przez cechy samego guza, jak również zależne od genetyki pacjenta, a także czynników zewnętrznych, np. składu flory bakteryjnej jelit, infekcji czy ekspozycji na promieniowanie słoneczne. Równowaga pomiędzy tymi czynnikami stanowi pewną bazę niezbędną do zrozumienia skuteczności odpowiedzi na immunoterapię nowotworów. Spośród licznych mechanizmów wykorzystywanych w terapii szczególną rolę odgrywają transfery limfocytów T, blokady punktów kontrolnych oraz szczepionki neoantygenowe. Dzięki specyficznym cechom ludzkiego układu odpornościowego, np. umiejętności rozpoznawania i eliminacji komórek nowotworowych, adaptacji podczas kancerogenezy czy pamięci immunologicznej, daje on wiele możliwości dla dalszego rozwoju terapii i nadzieję na długoterminową kontrolę nad chorobą.

Słowa kluczowe: układ odpornościowy, immunoterapia, nowotwory

INTRODUCTION

Cancer is a genetic disease, with the growth of tumor cells initiated and promoted by mutations in a group of genes known as drivers. This is just the beginning of a process of cancerogenesis, characterized by cellular, genetic and epigenetic alterations as well as the loss of normal cellular regulatory processes[1]. Mutanome – the set of all mutations – gradually increases, leading to the heterogeneity of tumor cells and the synthesis of novel proteins and peptide sequences (neoantigens)[2]. Their mutated epitopes (neoepitopes) are then processed and presented by the major histocompatibility complex (MHC) molecules, exposing the tumor cells to the risk of recognition by the immune system. Such immune recognition, undeniably defective in cancer patients, has become a muse for scientists all over the world, committed to pursuing a cure for cancer. Immunotherapy is, in fact, a type of treatment that exploits one's immunological system in order to cure a disease, including cancer. For many decades, the possible role of the immune system in cancer treatment remained unappreciated[3] not only due to the lack of appropriate analytic techniques, but also because of the undoubtedly disabled function of the host immunological response against the tumor. However, it was revealed already in 1950s that mice with syngeneic carcinogen-induced tumors are resistant to redeveloping tumor with the same cancer cells due to the development of adaptive tumor immunity[4]. In 1970s, it was proved that tumor-derived T cell clones recognize human tumor cell lines and correlate with adaptive immunity[5]. Yet, only in the 1980s, a detailed conformation of tumor neoantigens was revealed with the help of the newly introduced cloning techniques[6]. The studies classified the molecules into the tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). TAAs are either overexpressed in cancer tissues and arise from the tissue differentiation (e.g. HER2) or preferentially expressed by cancer cells, but not normal tissues (except for fetal or immune-privileged tissues – e.g. MAGE, NY-ESO-1, TPBG). TAAs are subject to some degree of central tolerance and lack complete specificity to the tumor. TSAs, on the contrary, arise as an effect of somatic gene mutations in cancer cells. As such, the resulting antigens are tumor specific and highly immunogenic, as they are not subject to the central tolerance[7]. Therefore, TSAs seemed an alluring target for immunotherapy, but the background for elaboration of new techniques was lacking. Thanks to recent advances in next-generation sequencing (NGS) technique, clear detection of all mutations occurring in cancer, allowing for identification of TSA sequences, has become feasible, on the basis of comparison of the DNA structure in non-mutated and cancer cells.

THE CANCER-IMMUNITY CYCLE

In the recent years, the pace of progress in cancer immunotherapy has increased. In 2012, scientists discovered that immune response in cancer is a series of carefully regulated events that may be optimally addressed not separately, but as a group[8]. This series was named a Cancer-Immunity Cycle and each of its steps was thoroughly examined, with a special focus on the stimulatory and inhibitory signals. It resulted in much broader understanding of the whole process, starting from the release of neoantigens and their recognition by dendritic cells, through activation of T cells and their infiltration of the tumor, up to the recognition and killing of cancer cells. This allowed a cancer immune response to be approached from a significantly wider perspective and, therefore, presented an innovative and immense spectrum for potential therapies. Next year showed that the defective immune protection in cancer patients results from inhibiting T cell responses by negative regulators in lymphoid organs (checkpoints) and in the tumor bed (immunostat function)[9]. Finally, one of the most crucial observations was that the Cancer-Immunity Cycle is aberrant in oncological patients. With all this knowledge, scientists concluded that immunotherapy may be an effective therapeutic option in a wide range of cancers, and exploiting the proper immunological anticancer response shall be a starting point of this approach. Therefore, the main goal in tailoring cancer-specific therapy is to revive the Cancer-Immunity Cycle, i.e. initiate the immunological response and allow for its undisturbed continuation by influencing various regulatory mechanisms, leading to effective killing of cancer cells[4]. However, the approach based on increasing the immunological activity poses a threat in the form of autoimmune inflammatory responses, which cannot be ignored[10].

The revelation of the complexity of mechanisms underlying the Cancer-Immunity Cycle has resulted in defining immunological and histological profiles of patients, responsible for suppressing or promoting anticancer immunity. Interestingly, it has been shown that such a profile is determined not only by intrinsic tumor properties (e.g. its' genetic composition) and patients' genetics (possible alterations in inflammatory signaling cascade), but also such extrinsic elements as gut microbiota, the presence of infection or exposure to sunlight. The balance between these factors, known as a cancer-immune set point, is a threshold that must be exceeded for a patient to respond to immunotherapy[3].

CANCER IMMUNOTHERAPY MECHANISMS

Among various types of cancer immunotherapy, we can distinguish an adoptive T cell transfer, checkpoint blockade and neoantigen vaccines.

Adoptive T cell transfer (ACT) is a new area of transfusion medicine involving the use of patient's own lymphocytes to mediate antitumor, antiviral or anti-inflammatory effects. The genetically modified autologous lymphocytes are reinfused into the patient and allow for achieving a substantial clinical benefit in otherwise treatment-refractory cancers. Three forms of ACT are being developed for cancer

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therapy: tumor-infiltrating lymphocytes (TILs), T cell receptor (TCR) T cells and chimeric antigen receptors (CAR) T cells[11].

TILs lead to durable clinical responses in patients with metastatic melanoma and other cancers[12–14]. TCR therapies were tested in patients with metastatic melanoma, with the use of TCRs recognizing shared tumor associated antigens such as HLA-A2, MART-1 and NY-ESO-1. The improved avidity and, therefore, improved immunological response rate was inextricably linked to greater off-tumor toxicity, caused by addressing the same antigen in normal melanocytes localized in the skin, eye and cochlea[15]. Although it seems that in shared antigenic targets such on-target, off-tumor toxicity is unavoidable and increases with the avidity, although some studies disagree with this conclusion[16] and suggest that developing therapies with TCRs recognizing tumor-specific neoantigens may be associated with milder safety. The CAR T cells therapy appears to be the most outstanding and developed among ACT therapies. The patient's T cells are transfected with a construct encoding an antibody against the tumor surface antigen, fused to the T cell signaling domains[17]. The procedure avoids the need for immunization and may even overcome the mechanisms of immune suppression by overwhelming the system through infusion of large quantities of modified T cells, promoting self-propagation of the Cancer Immunity Cycle. The method has recently been approved by the U.S. Food and Drug Administration (FDA) for treatment of refractory pre-B cell acute lymphoblastic leukemia and diffuse large B cell lymphoma on the basis of impressive clinical trials' results. Although the first clinical trials with the first-generation CAR T cells were unsatisfying, the second-generation, targeting CD19 and encoding for an additional costimulatory domains, proved to be an effective approach. CD19 is an antigen expressed solely on the surface of B cell lineage cells, indispensable for B cell advancement and with high expression levels in B cell – related malignancies. Interestingly, however, multiple myeloma, which is accompanied with low levels of CD19, is associated with a good response to the CD19 CAR T cell therapy. The possible use of the CAR T cells therapy was also investigated in solid tumors, but the results weren't favorable.

For all that, the question is whether this approach might be applied effectively in malignancies other than hematologic, whether the adverse consequences can be managed or eliminated and, eventually, whether large numbers of monospecific T cells won't face resistance due to antigenic drift[4]. This requires further studies.

The next type of immunotherapy is an immune checkpoint blockade (ICB). Its design and use are based on a hypothesis that immunological activity and response against cancer cells might be tuned down with negative immune regulation. Molecules taking part in such regulation are referred to as immune checkpoint inhibitors. There are many known particles transducing negative signaling, among which CTLA-4 and PD-1 gained the most attention. CTLA-4 is presented on a T cell surface after initial activation with two costimulatory signals in lymph nodes, and allows for competing with the CD28 molecule for the B7 ligands. The competition not only weakens the positive signaling of CD28, and lymphocyte activation, but also leads to the transduction of inhibitory regulation when the ligand is bound. Another possible step of inhibition takes place in a tumor microenvironment, where cancer cells present PD-L1 – a ligand for PD-1. PD-1 molecule is a negative receptor, which is presented by the T cells after recognition of a specific antigen by the TCR region. Therefore, blockade of CTLA-4 or PD-1 helps to avoid the suppression of antitumor response and overcome the adaptive immune resistance. There are a few monoclonal antibodies developed or currently tested in clinical trials. Ipilimumab, the first anti-CTLA-4 antibody was engineered in 2000 and in 2011 received the FDA approval for the treatment of melanoma. Other antibodies, used in the clinical practice include nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), avelumab (anti-PD-L1) or atezolizumab (anti-PD-L1). The most common indications include melanoma, non-small cell lung cancer or urothelial cancer, but the therapy seems promising in many cancer types, therefore numerous clinical trials are currently on-going.

Ipilimumab treatment significantly improves survival among patients with metastatic melanoma, traditionally considered as a fatal diagnosis, thus, puts a lot of hope in this new generation of cancer treatments. After 8 years since the first FDA approval, more data on the efficiency of checkpoint blockade therapies has been gathered. In malignancies, such as the Hodgkin's lymphoma, Merkel cell carcinoma or cancers with high mutation burden, checkpoint blockade allows for achieving the objective response rate (ORR) of 53% to 90%. However, in other diseases this therapy fails to lead to such high response rates: in renal cell carcinoma, gastroesophageal cancers or non-small cell lung cancer (NSCLC) the ORR ranges from 15% to 25%[18]. On the other hand, the frequency of rapid tumor shrinkage from single-agent anti-PD-L1/PD-1 antibodies ranges from 10% to 40%, depending on the disease type. One of the possible ideas to improve response rates is to combine PD-1/PD-L1, CTLA-4 blockade together or with different anticancer agents. Both approaches seem to have a mechanistic background as they have different targets. The combination of ipilimumab and nivolumab in metastatic melanoma resulted in ORR >50%, whereas single agent nivolumab treatment ORR was 35–40%[18,19]. However, when using multidrug treatment schemes, the problem of serious adverse effects is emerging. In cases of combined checkpoint blockade treatment, the risk of immune-related adverse effects might be up to 60%[18,20].

The response rates of checkpoint blockade might also be reduced by patient specific factors, such as a preexisting low antitumor T cell response, scarce infiltration of the tumor microenvironment or its immunogenicity. Checkpoint blockade is believed to result in longer responses,

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which remain significantly more durable when compared with other therapies. Nonetheless, there are cases of relapse due to resistance acquired as a result of impaired IFN-gamma signaling or defective antigen presentation[21]. About 40–60% and, in some malignancies, even higher percentage of patients will not benefit from ICB. This shows the need for identification of precise biomarkers, allowing for prediction of response. Such predictors would allow for using ICB only in selected patients, as the therapy has adverse effects, is expensive and, most importantly, there might be other treatment schemes more beneficial for patients who will not respond to immune checkpoint blockade. Both the human immune system and cancer cells are in a constant process of changing and adapting, which hinders the efforts of identifying relevant biomarkers. PD-L1 expressed on tumor cells is the most commonly analyzed biomarker for predicting the treatment response. Depending on cancer, high PD-L1 expression may be a positive or negative predictor. Even in malignancies, in which overexpression correlates with better response, not all of the patients with high levels of PD-L1 are going to respond to the therapy, as well as patients without expression of PD-L1 are able to achieve a significant response with ICB[20,22].

TUMOR ENVIRONMENT

Chen and Mellman[3,8] distinguished three phenotypes of tumor environment: the inflamed tumor (characterized by tumor infiltration by CD8+ T cells), the immune excluded tumor (the CD8+ T cells are present on the margin of the tumor, but do not penetrate the tumor efficiently), and the immune desert tumor (in which CD8+ cells are absent). A study showed that patients with immune-active microenvironment are more likely to achieve a better outcome[23]. However, it is worth noting that the immunity of tumor microenvironment is variable and chemotherapy treatment may induce higher activation of the immune system in the tumor[24].

Also, data from cancer DNA sequencing may be a significant biomarker as the mutational burden is known to correlate with better response rates in ICB therapy. Moreover, defects in the mismatch repair genes have been shown to be a positive marker of response to pembrolizumab in hereditary non-polyposis colorectal cancer (HNPCC) cases[22,25]. On the other hand, there are known cases of resistance to ICB due to mutations in JAK, JAK2 or beta-2-microglobulin[21].

T-CELL-MEDIATED RESPONSE

The importance of a T-cell-mediated response in cancer treatment led the scientists to attempt to create a vaccine, which would work similarly to the vaccines used for the prevention of contagious diseases. Recent advances in NGS and bioinformatics allowed for efficient mapping of the cancer mutanome and for choosing the most suitable targets for the vaccines. Choosing a few mutations as targets gives a chance to address the problem of antigenic escape. With positive results of mouse tests, there were 3 first human trials, conducted recently in melanoma patients. All three trials took different approach and created vaccines in distinct forms.

The first trial consisted of 3 patients with a resected stage III melanoma. The vaccine was prepared based on the dendritic cells. Prior to vaccination, patients were given ipilimumab. It proved neoantigen vaccine to be safe and able to promote neoantigen-specific T cell reaction[26]. The second trial was conducted in 6 patients with at least stage IIIB melanoma, who underwent surgery with curative intent. Each patient received 5 priming and 2 boosting doses of long peptide vaccine. After the median follow-up period of 25 months, 4 patients staged IIIB were free of any recurrences and 2 patients with lung metastases showed radiographic recurrences. After additional 4 doses of pembrolizumab, both patients achieved complete response. For comparison, complete response rate in disseminated melanoma was reported to be 6.1% for pembrolizumab and 1.4% for ipilimumab[27]. The last trial was conducted in 13 patients with at least stage III melanoma. The patients were given a vaccine consisting of a synthetic RNA, encoding the 10 targeted neoantigens. The study showed that 8 non-metastatic patients had no signs of recurrence during the follow-up period of 12 to 23 months. In 5 patients with metastatic disease, the vaccine enhanced the response to standard treatment. The study faced a significant problem, which has to be addressed in further trials - an escape mechanism of tumor cells, which occurred in one patient. It relied on the β2-microglobulin deficiency, leading to the lack of response to the vaccine and subsequent death of the patient[28].

Though the results obtained so far are promising, many questions remain to be answered, including the aspects of the most efficient vaccine formulation, which determines the way of administration of the vaccine to the patient. Other aspects include creating more efficient algorithms for choosing the best mutations to target, managing cross reactivity with wild-type antigens, achieving higher rates of immunization against chosen neoantigens or prevention of antigenic escape among the tumor lines. Based on the treatment response rates achieved by patients with metastatic diseases, it appears that combining neoantigen vaccines with checkpoint blockade might be an efficient treatment approach in more advanced cases. Such combination would allow for priming of new T cells and avoiding the negative regulation of inhibitory checkpoints[5].

POLYTHERAPY

Even though immunotherapy has been introduced into treatment schemes of a few cancers, there are still numerous malignancies, in which monotherapy with immunotherapeutic agent fails to achieve high response rates. In such situations, polytherapy, whether with chemotherapeutic

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or other immunotherapeutic drug, seems to be a possible solution[29,30], primarily in order to prevent the immune escape. Therefore, complementary therapies that reverse the immune suppression in the tumor microenvironment may play a key role in unleashing the full potential of a neoantigens-based cancer vaccine. For example, several studies have suggested the possible additive or synergistic effects between a cancer vaccine and checkpoint blockade[30]. Furthermore, mouse models showed that the dual blockade of both CTLA-4 and PD-1 pathways resulted in an additive response, allowing for more effective T cell activation, further augmented with a vaccine[30], which provides the scientific basis for clinical trials. Targeting other inhibitory receptors is actively tested in preclinical and clinical studies. Undeniably, however, higher response rates with multidrug schemes carry the risk of more serious adverse events[18,20].

CONCLUSIONS

The genuine features of the human immune system, such as specific recognition and elimination of cancer cells, adaptation to an evolving tumor and immunological memory seem to be a perfect combination to create a powerful weapon for long-term cancer control. Nevertheless, the exact understanding of immunological mechanisms in both tumor growth and cancer elimination requires more thorough studies and may lead to an enhanced efficiency of a wide variety of immunotherapeutic anticancer approaches.

Conflict of interest

Authors declare no conflicts of interest.

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