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AN ANALYTICAL RESEARCH ON THE MOLECULAR PHARMACOLOGICAL PERSPECTIVES OF THE PHARMACODYNAMICS AND PHARMACOKINETICS OF NEWER CANCER ONCOIMMUNOTHERAPEUTICS

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ABSTRACT

With the rapid development of oncoimmunology, immunotherapy has been approved for the treatment of multiple cancers and has achieved surprising clinical outcomes in recent decades. This analytical research was conducted on the molecular pharmacological perspectives involving the pharmacodynamics and pharmacokinetics of the different types of newer oncoimmunotherapeutic treatment modalities, under various phases of clinical trials, for the treatment of pre-cancers, malignancies and metastases.

KEYWORDS: Cancer oncoimmunotherapies, cell based immunotherapies, oncolytic virus immunotherapies, neoantigen vaccines, nanoparticle-based approaches, polyepitope DNA vaccines, cancer pharmaco-chemo-immuno-therapeutics.

INTRODUCTION

With the rapid development of oncoimmunology, immunotherapy has been approved for the treatment of multiple cancers and has achieved surprising clinical outcomes in recent decades. Yet, not all patients respond to cancer immunotherapy. Moreover, the main approach to delivering immunotherapy is through systematic administration, which may result in many immune-related adverse events, because of off-target effects and as many drugs cannot reach solid tumors at sufficient levels, especially when facing many delivery barriers. Therefore, developing other advanced treatment technologies to improve the safety and efficacy of immunotherapy is urgently required. Some of these novel technologies are described below.

OBJECTIVES

This analytical research was conducted on the molecular pharmacological perspectives involving the pharmacodynamics and pharmacokinetics of the different types of newer oncoimmunotherapeutic treatment modalities, under various phases of clinical trials, for the treatment of pre-cancers, malignancies and metastases.

METHODS, RESULTS, DISCUSSION

Cell-based immunotherapies

T cells are the major type of cells that directly kill tumor cells in the TME. Cell-based immunotherapy is mainly referred to as chimeric antigen receptor (CAR)-T cell immunotherapy, in which the T cells are collected from the patient (autologous) or a healthy person (allogenic), the cells are genetically engineered to express an artificial CAR specifically targeting an antigen presented on tumor cells, and then the cells are administered in patient to eradicate tumor cells. The first experimental target was CD19, which is mainly expressed on B cell leukemia and lymphomas. The FDA approved anti-CD19 CAR-T cells for the treatment of refractory pre-B cell acute lymphoblastic leukemia and diffuse large B cell lymphoma, which revolutionized cancer immunotherapy. Moreover, the application of CAR-T cells is not limited to only CD19 and it has been extended to CD22 and BCMA. However, cytokine release syndrome is frequently observed during treatment. Secondly, although CAR-T cell therapy has achieved excellent results in hematological tumors, it has not been as effective in solid tumors. To overcome this limitation, one study tried to use bioengineered polymer scaffolds, which when implanted near or at the resection sites of tumors were able to stimulate and expand tumor-reactive T cells, producing a curative effect in mouse models of

solid tumors. In addition, scientists are also investigating several novel methods such as synthetic APCs and nanoparticle-functionalized T cells. Nevertheless, more evidence is required to show whether these methods can be further developed and introduced into clinical trials.

Although CAR-T cell immunotherapy has exhibited impressive results in hematological malignancies, it usually does not provide enough value in solid tumors. In contrast, TCR-engineered T (TCR-T) cells may show greater promise in solid tumors because engineered TCRs consist of a glycoprotein alpha-beta chain heterodimer that can bind to peptides presented by MHC molecules. As a result, TCR-T cells can recognize both surface proteins and intracellular proteins, targeting many more antigens and penetrating tumors better than CAR-T cells. Most of the clinical trials on TCR-T cells are still in phase 1 or phase 2, and the cost and time-consuming process of TCR cloning limit the broad application of TCR-T cell therapy.

Furthermore, several researchers believe that a combination of CAR-T and TCR-T cell immunotherapies will have therapeutic effects on solid tumors in the future because their mechanisms of action and resistance are completely different from those of traditional CAR-T cell immunotherapy. Similarly, to overcome the challenge of solid tumors not satisfactorily responding to CAR-T cell immunotherapy, a study focused on macrophages, which are very abundant in the TME of many types of solid tumors. In a study,chimeric antigen receptor macrophages (CAR-Ms) were produced, that secreted proinflammatory cytokines and upregulated antigen presentation, ultimately enhancing their antitumor ability. In humanized mouse models, CAR-M therapy significantly diminished the TMB and prolonged OS. However, there are still many limitations in CAR-M therapy. For example, CAR-Ms could not proliferate *in vitro* or *in vivo*, and the biodistribution of CAR-Ms after systemic administration also largely influenced the response rate.

DCs are the most powerful APCs in the human body and have garnered considerable attention in the development of novel therapeutic cancer vaccines. The manufacture of DC vaccines generally starts with the isolation of autologous DCs, followed by exposing them to an appropriate source of tumor-associated antigens (TAAs) *ex vivo* and then, refusing them back into the patient. A series of clinical trials have already been undertaken in patients representing many types of cancers, which demonstrated the safety and therapeutic profile of DC vaccines. However, DC vaccination may have limitations as monotherapy because of the immunosuppressive microenvironment, so the combination of DC vaccination with other therapies, such as ICB, chemotherapy, and radiation therapy, may enhance antigen-specific antitumor immunity.

Oncolytic virus immunotherapies

Scientists have invented various vaccines against viruses to prevent oncogenesis, but they are also currently using viruses as immunotherapy. ‘Cold tumors’ usually do not respond well to immunotherapy. To overcome resistance to ICIs, there are many combination therapies under investigation, including approaches turning ‘cold tumors’ into ‘hot tumors’. Due to their abilities to infect tumor cells and propagate within these cells, oncolytic viruses (OVs) can selectively kill cancer cells, resulting in the release of TAAs, additional DAMPs, viral pathogen-associated molecular patterns (PAMPs), and other molecules, such as cytokines, to induce an antitumor immune response. The first approved OV therapy was talimogene laherparepvec (T-VEC), which is based on a type 1 herpes simplex virus (HSV-1). With the deletion of ICP34.5 and ICP47, T-VEC can specifically replicate in and lyse tumor cells, ultimately inducing local and global antitumor immunity. A phase III clinical trial investigating the efficacy and tolerance of T-VEC successfully treated advanced-stage melanoma. However, this current OV therapy works only in a few select types of tumors. Although there are many novel methods of drug delivery under investigation, the dose-effect relationship of OVs cannot be predicted easily due to their self-replication. Moreover, the application of OV therapy in combination with other immimmunotherapies remains in the experimental stage.

Neoantigen vaccines

In addition to OV administration, increasing the expression of neoantigens is another way to turn ‘cold tumors’ into ‘hot tumors’, which could induce specific antitumor immune responses. Among two successful cases of personalized neoantigen-based tumor vaccines for the treatment of advanced melanoma, one was about an RNA-based polypeptide vaccine that produced sustained progression free survival (PFS) in over 60% (8/13) of patients. The other was about a vaccine that targets up to 20 predicted personal tumor neoantigens which led to no recurrence in nearly 70% (4/6) of patients for 25 months. In a similar study, personalized neoantigen vaccines was generated based on NGS with their in-house pipeline iNeo-Suite. This was the first pan-cancer clinical study concentrating on personalized neoantigen vaccine monotherapy that showed promising feasibility, safety, and efficacy. Most anticancer DNA vaccines, both past and present, immunize using nonmutated TAs. However, these antigens are often present in normal or germline tissues, which can prevent a strong immune activation because of immune tolerance. Several clinical trials using nonmutated TAs have failed to demonstrate beneficial effects compared with the standard of care treatment. In contrast, neoantigens are the result of tumor-specific DNA alterations that create new epitopes. Due to their specific expression in cancer tissue and the potential lack of side effects, they represent ideal targets against cancer and can be used in the design of cancer vaccines. They can also turn “cold” tumors into “hot” ones and mediate the

upregulation of PD-L1 in the TME, thus extending the applicability of the anti-PD-1/PD-L1 immunotherapy. Neoantigens are presented by APCs to CD4 type and CD8 type T cells to activate an immune response. They are highly tumor-specific and, therefore, they represent an attractive immunotherapy target. It is expected that they are not affected by T cell tolerance, as they may be recognized as non-self by the host immune system and, thus, generate a specific anti-tumor response. Their identification starts with exon sequencing from a tumor biopsy. Then, mutations are identified compared to whole exome data from normal tissue. Prediction algorithms select those antigens that are recognized by MHC class I or II. Finally, *in vitro* and *in vivo* studies validate their ability to stimulate the CD8 type immune response, especially a CD4 type response. However, not all peptides are immunogenic, and identifying which mutations are targeted by the immune system is currently a subject of great interest. Hence, the prediction of the immune response to neoantigens needs to be optimized. Assessing the immunogenicity of each neoepitope is not reasonably applicable on a large scale. Current computational approaches are being refined to improve the accuracy of neoantigen identification. Integrated pipelines will need to be developed beginning with tumor genomic characterization, variant analysis, and the accurate prediction of which mutations are likely to give rise to tumor-specific neoantigens. Other hurdles are associated with the use of personalized neoantigens for cancer immunotherapy, such as the manufacturing time. The median period for the discovery and production of a personalized vaccine is approximately 4.5months. In particular, the time from the selection of mutations to vaccine release ranges from approximately 89–160 days. This amount of time has to be reduced to cure patients with metastatic disease. Another issue concerns the genetic heterogeneity of tumors. Thus, targeting a unique neoantigen would probably lead to the selection of antigen non-expressing tumor cells. It has been demonstrated that the use of a poly-epitope neoantigen RNA vaccine encoding up to 10 neoantigens was effective in 8/13 melanoma patients who were completely tumor-free after one year. Compared to RNA and peptide vaccines, DNA vaccines seem to elicit a more potent CD8 type response against the encoded neoantigens, making them more attractive for cancer vaccination. Hence, once identified, the neoantigen can be cloned into a DNA vaccine. This personalization permits the design of cancer vaccines tailored to each patient.

Nanoparticle-based approaches

To date, a diversity of immunotherapies, including ICIs, ACTs, tumor vaccines, OVs and cytokine therapies, have been established. The effects of these therapies rely largely on their interactions with targeted molecules or cells, so an efficient delivery technology could strikingly improve the effect and safety of these therapies. A typical example of nanoparticle-based approaches is nanoparticle programmed CAR-T cells. Nanoparticles that encapsulate tumor CAR-encoding DNA recognize circulating T cells through CD3 molecules in the blood, releasing the DNA into the T cells to achieve sufficient cellular CAR expression to eradicate tumor cells. This method has achieved great success in mouse models of B cell lymphoblastic leukemia, which provided a novel idea for making CAR-T cell therapy possible in hospitals without the need to engineer T cells *ex vivo* in a special laboratory. Moreover, another study used nanoparticles to deliver tumoral mRNA in vivo. Researchers have used lipid based nanoparticles to package mRNA transcripts encoding tumor neoantigens. Systemic administration into multiple mouse models of established tumors then led to the expression of TAAs by local APCs and subsequently induced durable type I IFN-dependent antigen-specific immunity. Nanotechnology can improve the safety and efficacy of immunotherapy by better controlling the dose, location, release, and penetration of immunotherapeutic drugs or cells as well as by optimizing the treatment process. As a consequence, nanotechnology could make tumor immunotherapy more comprehensive and more effective. They could enhance the immunological function of our body through different mechanisms, and they are powerful complements for existing immunotherapies. Chimeric DNA vaccines are vaccines that encode xenogeneic antigens. They are proteins or peptides derived from different species in which the sequence is significantly homologous with the self-ortholog. The subtle differences between the epitopes of the orthologue and the native protein elicit T and B cell responses against the xenoantigen. Hence, xenogeneic antigens are recognized as “non-self-antigens”, thus circumventing immune tolerance while preserving an optimal homology to allow T cell recognition. During recent years, different studies have demonstrated the higher efficacy of xenogeneic antigens compared to autologous antigens. A complex DNA vaccine construct that delivers several xenogeneic epitopes dramatically increased the CTL antitumor activity. The efficacy of DNA xenovaccines was also tested in dogs, leading to the approval of the first xenogeneic DNA vaccine against human tyrosinase, Oncept, for the treatment of oral malignant melanoma in dogs. It is also possible to design hybrid plasmids, which code for chimeric proteins that include both xenogeneic and homologous antigen domains. In this type of plasmid, the xenogeneic moiety can circumvent immune tolerance and induce a more potent cellular response, while the homologous sequence can stimulate the activation of a broader immune response. Indeed, the chimeric protein produced by transfected cells can be taken up by DCs, thus activating the T cell immune response but it can also be recognized and internalized by B cells. In a study, it was found that the plasmid encoding the chimeric neu-Her-2 antigen was superior to both the fully autologous and the fully xenogeneic against ErbB2 type tumors. Starting from these results, other DNA vaccines were constructed by shuffling genes from mouse, rat, human and other species, improving the antigen immunogenicity and vaccine efficacy. DNA

xenovaccination has also been tested in the clinic in melanoma patients, with encouraging results, and one clinical study (NCT00096629) using the human and murine prostate-specific membrane antigen is ongoing.

Polyepitope DNA vaccines

An advantage of DNA vaccines is the possibility of delivering several antigen genes in the same construct, at the same time and with the same delivery method. The presence of immunodominant and unconventional epitopes simultaneously delivered by a polyepitope DNA vaccine can induce a broad CTL response specific to multiple antigens. In this way, it is possible to overcome the antigen mutation or deletion by tumor cells, the variation or absence of the appropriate T cell repertoire and the MHC haplotype in patients. When designing a poly-epitope DNA vaccine, many parameters should be considered. First, the competition for antigen recognition at the surface of the APC and the affinity of the selected epitopes for MHC molecules should be considered. A study demonstrated that the use of an MHC class I polyepitope vaccine leads to the preferential expansion of CTLs with a single immunodominant specificity. Moreover, the affinity of the selected epitopes for MHC molecules and transporters could influence the CTL immunodominance and the consequent immune response. Second, although the CD8 T cell response has been considered to be the main protagonist in the antitumor immune response resulting from vaccination, the insertion of an epitope/antigen recognized by CD4 T cells into a DNA vaccine could activate a broader and stronger immune response. Several studies suggest the importance of the CD4 T cell population for cancer immunotherapy. Recently, it has been demonstrated that CD4 T cells recognize a higher number of neoantigens than previously known and can generate potent antitumor responses. Hence, a coordinated CD4 and CD8 response is necessary for the complete eradication of a tumor. T helper (Th) peptides have already been used in combination with DNA vaccines to increase the activation of Th cells, thus further eliciting the CTL immune response. An example of a Th epitope is the pan DR epitope (PADRE). This synthetic Th epitope, encoded in a DNA vaccine and administered with an antigen-encoding plasmid, increased the number of antigen-specific CD8 T cells, resulting in potent protective and therapeutic antitumor effects. Other studies demonstrated that a PADRE-encoding DNA generated CD4 Th1 cells that play an important role in maintaining long-term memory responses, helping the activity of CD8 Tcells. Many techniques have been developed to find new epitopes. These studies led to the identification of NY-ESO-1, MelanA/MART-1, SSX4, MELOE-1 and TRAG-3 in melanoma, EphA2 and MAGE-6 in renal cell carcinoma, CEA, MAGE-3 and telomerase in lung carcinoma, TRAG-3 in breast carcinoma, and NY-ESO-1, p53 and SSX4 in ovarian cancer, among others. Some of these tumor antigens recognized by CD4 T cells belong to the same categories as those recognized by cytotoxic CD8 Tcells. Finally, it is important to identify the most immunogenic epitopes derived from tumor antigens. New *in silico* techniques are being developed to improve the prediction of epitope immunogenicity to design a poly-epitope vaccine. They not only consider the binding affinity to the MHC and the different HLA subtypes but also the conformation and interaction with the HLA, immunodominance *vs* tolerance, and similars. Many recent preclinical studies have investigated the use of polyepitope DNA vaccines to reach a broad immune response. As a result, an increased IFNg production, a higher Th and CTL response, and a general decrease in the tumor growth rate and metastasis formation were observed in different types of cancer models. Some preclinical studies focus on the HPV model, using DNA vaccines encoding E6 and E7 molecules, or E7 with a helper epitope. Another example is SCT-KDR2, which encodes the mouse â2microglobulin and KDR2 (VEGFR2 antigen peptide) and MHC class I H-2Db, in a B16 melanoma tumor model. Additionally, many clinical trials are testing the safety and efficacy of polyepitope DNA vaccines, such as NCT02348320 and NCT02157051 for breast cancer, NCT02172911 for cervical cancer, and NCT01322802 and NCT03029611 for ovarian cancer. In particular, in the clinical studies NCT02348320 and NCT03199040, a personalized polyepitope vaccine against breast cancer is being used, as well as in the NCT03122106 for pancreatic cancer, and the results will help to establish the relevance of this vaccine strategy. This would address tumor heterogeneity and the loss of immunogenicity associated with TAAs, which accounts for the failure of the current anti-cancer treatments. A good option to further optimize the efficacy of cancer DNA vaccination could be the combination of the 3 cited approaches, designing a poly-epitope chimeric vaccine containing specific neoantigens. In the clinic, this could reduce the number of nonresponding patients by developing a stronger and more complete immune response.

CONCLUSION

Therefore, this research has analytically unraveled the several molecular perspectives of the pharmacodynamics and pharmacokinetics of the newer oncoimmunotherapeutic treatment modalities, for the treatment of pre-cancers, malignancies and metastases.

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1. Medical Literature Database.