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Review



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Editorial note：*Yu-quan Wei et al. "Translational research advances in cancer therapy" provide an overview from the respects of immune, gene, antiangiogenic therapies and molecular targeted approach: A great progress has been made for the immune therapy, as lots of tumor vaccines and antibody drugs are in phase II/III clinical trials. Several gene therapy protocols have been approved. The effects of antiangiogenic drugs on chemotherapy and radiotherapy are also observed. The combination of molecular targeted therapy and immunotherapy might become a cutting edge of transformational researches. In addition, the authors put forward that tumor biotherapy has both the population-based and individualized features, and as a result, raise the new challenges for both effect and safety evaluations. In order for a better communication and cooperation, the researchers should be cross-disciplines orientated with a combined approach of oncobiology, immunology, as well as clinical practices.*

Translational research advances in cancer therapy

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Abstract Biotherapy is the fourth modality of cancer therapy and the important field of medical translational researches. Cancer biotherapies, including tumor vaccines, gene therapy, anti-angiogenic therapy, targeted therapy, and etc have made great progress in clinical translational research in recent years. Simultaneously, the new challenges that clinical investigations of cancer biotherapy have brought to translational researches will be discussed in the mini review.

Key words cancer biotherapy, translational research, tumor vaccine, gene therapy, anti-angiogenic therapy

Biotherapy of human diseases has become the high-light of current medical research with a promising future both at the bench-top and bed-side level. For the cancer therapy, biotherapy has entered the mainstay of treatment modalities following surgery, radiotherapy and chemotherapy. Cancer biotherapy (biological therapy), also "advanced therapy" in Europe [1], initially was to against tumor cells by eliciting or restoring immunity of the body. However, the concept has changed to cover other strategies such as small molecular kinase inhibitors [2－4]. Generally, tumor biotherapy includes but is not limited to immune therapy (tumor vaccine, antibody, immune cells and cytokine), gene therapy, anti-angiogeneic therapy and kinase inhibitors, and some integrated fashions as well.

Nowadays, insights into the molecular network underlying the biological behavior of tumor provide new opportunities

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for the treatment. The last decade witnessed the rising of the "bench to bedside" idea which was proposed as a translational research to integrate the basic and clinical study. This idea also facilitates the clinical translation for cancer biotherapy.

1 Immune therapy

Scientists have long pursuited to translate the success of vaccine in the field of contagious disease to that of cancer. The effort was mostly in vain until the discovery of the first tumor specific antigen MAGE-1 in the 1990s. Since that time, the first approved tumor vaccine Melacine for malignant melanoma, became available in Canada in the year of 2000. Then follows melanoma vaccine M-Vax in Australia and renal cancer vaccine Oncophage in Russia. In April 2010 came the milestone vaccine Provenge for prostate cancer. Provenge is based on the fusion of PAP which is a tumor marker for prostate cancer and GM-CSF. Provenge provides the patients with advanced prostate cancer a survival benefit of 4.2 months. Currently, over 100 tumor vaccines are in phase II/III clinical trials.

The potential of antibody drug has been fully accepted. The antibody drug is originated from the monoclonal antibody technique dated back to 1975 by Kohlor and Milstein. In 1995, the first mouse monoclonal antibody against EpCAM was approved in German to treat colon cancer but failed to show effects later on [5]. In 1997, the first chimeric antibody against CD20 MabThera was approved by FDA to treat refractory low differentiated or follicular B-cell non-hodgkin lymphoma. In 2005, the first fully humanized antibody against EGFR Panitumumab was approved by FDA to treat colorectal cancer. Till 2009, antibody drug constitutes 30% of bio-tech drugs. The R&D of bifunctional and multifunctional antibodies has become a new hotspot in recent years. The bifunctional antibody targeting both CD3 and Her2 proves to be safe in a phase I trial (ASCO 2011, abstract no 2548). The trifunctional antibody Catumaxomab improves the QOL of patients with malignant ascites and provides longer survival (ASCO 2011, abstract no. 2512, 9113)[6]. Maybe in the near future these novel antibody drugs will enter the clinic as well.

Breakthrough has been achieved in cell therapy. Tumor-infiltrating lymphocytes (TIL) provides object response of 70% in patients with progressive melanoma[7, 8]. Chimeric Antigen Receptor (CAR) modified T-cells have specific killing activity with immune memory but without MHC restriction. These engineered T-cells bring significant survival benefits in patients with chronic lymphoid leukemia [9, 10]. This strategy produces specific CTL while independent on antigen-presentation, and may contribute to individualized medicine.

2 Gene therapy

Gene therapy has long been proposed for cancer which is thought to be a genetic disease. However, due to the complex multiple genetic events in cancer, not only the expression or regulation but also the functional alteration post translation, it is extremely difficult for gene therapy. Less than 10 gene therapy protocols in III phase clinical trial are retrieved from Clinicaltrials. gov. The gene therapy drug in China Gendicine (recombinant Ad-p53) to introduce wild-type p53 into tumor cells have proven effective [11]. However, it has met its obstacles when on market. Recently emerging data from early phase clinical trials still provide promise in this field. A siRNA-based drug targeting VEGF ALN-VSP02 proved to be safe and effective[12]. Trabedersen, the anti-sense oligonucleotide for TGF-b showed promising effects in pancreas cancer, melanoma and colorectal cancer in the phase I/II trial (ASCO 2011, abstract no. 2513). Gene therapy can also be used to modify the tumor cells, immune cells, or be integrated into the oncolytic virus [9, 13]. CAR modified T cell for cancer therapy is an important model of gene therapy. In addition, tumor cell vaccine modified by the anti-sense TGF-β has successfully entered phase III clinical trial due to the promising results in phase II clinical trial [14]. Usually the translational product in vivo is required to achieve the final therapeutic effects, and this will undoubted influence carry-out of gene therapy. It seems there is still a long way to go for gene therapy.

3 Antiangiogenic therapy

Since Prof. Folkman's pointed that tumor growth depended on angiogenesis was proposed and confirmed in 1971, antiangiogenic therapy has been an important field of cancer research[15]. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), was the first antiangiogenic drug approved by FDA in 2004 and has been used for colon cancer treatment for years. So far, a great number of antiangiogenic drugs have been on sale such as cetuximab, nimotuzumab, endostar, thalidomide, et al. Moreover, many small molecular multi-targeting inhibitors such as sorafenib, sunitinib also have a direct antiangiogenic effect. However, single antiangiogenic drugs can not obtained satisfied effects, since the mechanisms of these drugs are suppressing tumor growth and metastasis by inhibiting or destroying tumor vessels not killing tumor cells directly. Therefore, antiangiogenic therapy with concurrent chemotherapy and radiotherapy are needed to improve therapeutic effect in cancer therapy, and these combined treatments have been

used in clinical practices for the moment[16-20]. In recent years, researches showed that the increased therapeutic effect of antiangiogenic drugs on chemotherapy and radiotherapy was depend on normalization of tumor vessels[20-22]. In addition, there existed time window has been observed in the process of normalization of tumor vessels[23]. For this reason, better therapeutic effect can be obtained by optimizing timing sequence on antiangiogenic drugs and chemotherapeutic drugs.

4 Molecular targeted therapy

Molecular targeted drugs include monoclonal antibodies and small molecular inhibitors. With the development of tumor biology, current cancer treatments have developed into interventions against known targets with purposes. These targets are always important molecules in tumor cell signaling pathways which play important roles in carcinogenesis. Currently, many tumor therapeutic targets have been found in basic biological researches and confirmed in clinical practices; this is helpful to accelerate the translational research between basic and clinical study and development of new drugs. Take EML4-ALK fusion gene which was found in lung cancer patients in 2007 for instance [24]. Because previous studies had proven that ALK was closely related to tumor cell survival, proliferation and metastasis, the similar effect of EML4-ALK fusion gene in lung cancer was soon confirmed by basic studies[26]. The specific inhibitor, crizotinib, was quickly developed and subsequently approved by FDA for clinical use in August 2011[27]. It only takes 4 years to complete this process and is a success profile of translational researches.

It is controversial whether molecular targeted therapy can be classified into biotherapy. Monoclonal antibodies and small molecular inhibitors, unlike traditional cytotoxic chemotherapeutic drugs, produce their anti-tumor effects by intervening or blocking important biological signals. Therefore, treatments with monoclonal antibodies or small molecular inhibitors were included into molecular targeted therapy and regarded as a part of biotherapy by some institutions and researchers in recent years[2-4, 28]. In fact, recent researches showed that antibodies and small molecular inhibitors could influence not only tumor cells but also immunocytes or immune microenvironment and modulate the host immune response[29, 30]. Thus, the combination of molecular targeted therapy and immunotherapy might become a cutting edge of transformational researches on cancer biotherapy in future.

5 Challenges for translational research

Considering that tumor biotherapy possesses both the feature of population and individuation, in clinical investigation and application, it raised new challenges to biotherapeutic products, patient groups, clinical therapeutic effect and safety evaluation. Firstly, in clinical investigation, the activity and therapeutic effect of both cell products and vaccines need to be individuation. For example, in vaccine research, it is not only necessary to validate its immunological activity, but also the antitumor effect [31]. To rationally evaluate the vaccine effect, we may need to extensively introduce new techniques into the evaluation process in clinical research. For example, the tetramer technologies are used to evaluate tumor vaccine. Second, most tumor biotherapeutic products do not induce tumor killing and difficult to observe direct tumor recession. In this situation, new markers and methods are needed to evaluate the therapeutic effect. For the past few years, the molecular image may be an important development direction [32, 33]. Third, in tumor biotherapy, both therapeutic target and their effects usually count on the detection of tumor biomarker. The biomarker discovery, validation, and clinical application have become an important filed of translational research [34, 35]. Fourth, considering that most tumor biotherapy does not cause tumor diminution or regression, currently, they could not be used as an independent clinical therapeutic method. Thus, how to integrate biotherapy into the present therapeutic modalities to achieve the best therapeutic effect becomes a major trend and challenge for the clinical application of biotherapy. Anti-angiogenic therapy has acquired essential progression and some tumor vaccines have been integrated in the clinical test session, for example, the phase III clinical trial of MAGRIT on MAGE-A3 positive patients with lung cancer. However, it still needs to pick out more optimized project through abundant translational research.

6 Conclusion

The translational research of cancer biotherapy has achieved important progression in the past few years, and series of tumor therapeutic products are used in clinical treatment. Owing to the intensive researches on oncobiology, the development of biotechnology and strengthen of translational investigation from basic to clinical, tumor therapy has entered a stage of rapid growth and integration. In recent years, China put great focus on the development of biomedicine. Both the he "eleventh five-year plan" and "twelfth five-year plan" give great support on it. Under the circumstances, tumor biotherapy has made much progress. In the aspect of immunotherapy, gene therapy, antibody therapy, anti-angiogenic therapy and molecular targeted drug, we have several new drugs of independent intellectual property right which have entered clinic or the phases of clinical trial. However, there are

still certain gaps when compared with the developed countries, and it is urgent to strengthen the translational research of biotherapy. To develop high quality translational research of biotherapy, it does not only need to enhance the cross-talk of "bench to bedside", but also raised new demands for the scientists who work in basic research field and oncologists. Aside from the cutting basic researches in oncobiology and tumor immunology, scholars that join into the translational research also need to be familiar with the challenges from clinical practice. Only in this situation, basic research and clinical research could communicate and cooperate thoroughly, and the innovation and transformation of biotherapy can be accelerated.

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