Translational medicine promising personalized therapy in oncology

Yi-Xin ZENG (✉)^{1,2}, MD, PhD, Xiao-Shi ZHANG^{1,3}, MD, PhD, Qiang LIU (✉)^{1,2,3}, MD, PhD

1 State Key Laboratory of Oncology in South China, Sun Yat-sen University, Guangzhou 510060, China

2 Experimental Research Department, Sun Yat-sen University, Guangzhou, Guangdong 510060, China

3 Cancer Biotherapy Center, Sun Yat-sen University, Guangzhou 510060, China

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Translational medicine has newly emerged to bridge the gap between bench-related basic science research and bedside clinical practice. From early diagnosis to late-stage disease treatment, translational medicine has transformed the clinical practice by making personalized medicine possible. Attributing to the progress in translational medical research, cancer therapy has evolved from non-specific cytotoxic drugs against both tumor and normal proliferating cells to more specific small molecule chemical and immunotherapy approaches. Small molecular agents are directed at unique pathogenesis of cancer cells, whereas immunotherapeutic agents target the cancer immune response. Both approaches aim to produce less toxicity with high effectiveness. Therapeutic regimens with these agents in biomarker-classified sensitive populations promises a personalized approach in modern oncology. Here we use targeted cancer therapy as an example to elucidate translational medicine in transforming the oncology practice. Targeted cancer therapy using chemicals of low molecular weight, monoclonal antibodies, or polypeptides to interfere with specific signal pathways in cancer cells inhibits cancer progression. Clinical evidence has demonstrated that targeted cancer therapy has a promising potential not only in killing cancers but also by inducing cancer cells to differentiate into normal cells, leading to patient cures. Furthermore, targeted cancer therapy leads to potent inhibition of tumorigenic signals. Delaying rapid cancer progression makes the patients “survive with cancer,” thus making cancer a manageable chronic disease in the future, similar to diabetes and hypertension. This editorial opinion reviewed the theory, features, and future direction of molecular target therapy.

Bench to bedside translation in the development of targeted cancer therapy

Every patient with cancer is unique in clinical presentation, prognosis, tumor response, and tolerance to treatment. This is in addition to differences in risk of recurrence, second malignancy, and long-term complications of treatment. Yet, only recently has bench side genomic study begun to reveal the biological heterogeneity of human cancer and the inter-individual variations in the human genome to enable a more personalized approach to cancer treatment. With advanced basic scientific technology enabling the interrogation of the cancer genome and the detection of variations in germline DNA, oncologists are more confident now than ever before to match personalized treatment with cancer characteristics. This means selecting the most appropriate drug type and dosage for each patient, thereby reducing the toxicity and enhancing the effectiveness of the treatment. However, the common implementation of personalized cancer therapy is currently restrained by limitations in our understanding of cancer biology and the ability to identify molecular targets that are distinct to cancer proliferation and progression. This opinion reviews the historic progression of targeted cancer therapy, and explores some of the challenges and opportunities in developing personalized treatment for patients with cancer.

Two milestone revolutions occurred on the road to cancer treatment in the past century. One was the theory of radical resection raised by Halsted in 1890 and the other was the combination of chemotherapy with radical resection (adjuvant or neoadjuvant chemotherapy) by Fish in the 1970s. Since then, little progress had been made in cancer treatment until the emergence of molecular targeted therapy. In the late 20th century, since the systemic biological perspective has been integrated in cancer research, cancer was soon recognized as a systemic disease involving multiple factors and steps. Mutations in proto-oncogenes, deletion of cancer suppressor genes, or deregulation of gene expression cause cancer genomic instability, which further leads to abnormal biological behavior of cancer cells, such as: (1) self-sufficiency in growth signals, (2) insensitivity to antigrowth signals, (3) evasion of programmed cell death (apoptosis), (4) potential for limitless replication, (5) sustained angiogenesis, (6) tissue invasion and metastasis, and (7) immune escape. Targeted cancer therapy, which is fundamentally different from traditional chemotherapy, uses small molecules, monoclonal antibodies, or polypeptides to interfere with specific signaling pathways that mediate the biological behavior of cancer cells, thereby inhibiting cancer development. Chemotherapy uses chemicals to directly damage DNA or impair mitosis, thereby inducing cell death. However, its non-selectivity in distinguishing normal and cancer cells generates side effects that often limit the strength and frequency of treatment. Chemotherapy not only impairs the functions of important organs such as the heart, liver, lungs, kidneys, and bone marrow, but also suppresses the immune system, thus impairing the self-protection mechanisms against cancer. Furthermore, chemotherapy increases genomic instability in cancer cells, which causes rapid adaption to chemotherapy drugs. Moreover, this instability may lead to the generation of a small population of self-renewing and drug-resistant cells, that is, the “stem cell-like cancer cells.” The adverse events and drug resistance caused by chemotherapy result in the discontinuation of cancer treatment. Conversely, targeted cancer therapy specifically targets the abnormal signaling pathways in cancers and has high selectivity, low toxicity, and high therapeutic index, thus allowing long-term use and the possibility of transforming cancer into chronic diseases such as hypertension and diabetes.

Since 1997 when the monoclonal antibodies trastuzumab (Herceptin) and rituximab (Mabthera) were approved to treat metastatic breast cancer and diffuse large B-cell lymphoma, the history of targeted cancer therapy is only slightly more than a decade old. At present, more than dozens of molecular targeted agents have been approved to treat solid cancers, as well as several others for hematologic malignancies. Overall survival is regarded as the gold standard for determining therapeutic response. Targeted cancer therapy improves survival in two ways. First, by inducing cancer cell differentiation, or when used in combination with traditional surgery, radiotherapy, and chemotherapy, targeted cancer therapy improves the five-year survival rate of cancer patients and results in a higher remission rate. Examples include all *trans*-retinoic acid (ATRA) and arsenic trioxide (As_2O_3) for acute promyelocytic leukemia (APL), trastuzumab for breast cancer, rituximab for lymphoma, imatinib for gastrointestinal stromal cancers and chronic myelogenous leukemia (CML). Second, by slowing cancer progression, targeted cancer therapy can prolong the survival and improve the quality of life of patients treated with palliative therapy. This class includes erlotinib for non-small cell lung cancer and pancreatic cancer; gefitinib for non-small cell lung cancer; temsirolimus for renal cell carcinoma; bevacizumab for colorectal carcinoma, non-small cell lung cancer, breast cancer, and renal cell carcinoma; cetuximab for colorectal carcinoma, as well as head and neck squamous cell carcinoma; lapatinib for breast cancer; sorafenib for renal cell carcinoma; sunitinib for renal cell carcinoma and gastrointestinal stromal cancers; YH-16 for non-small cell lung cancer; and bortezomib for multiple myeloma. The clinical benefit of targeted cancer therapy is being enriched and expanded as the bench to bedside translation of medical practice continues.

Current success in targeted cancer therapy

“Differentiation therapy” opens a new horizon for cancer treatment

Compared with normal cells, some types of cancer cells are less differentiated, which is one of their important biological characteristics. Thus, this type of cancer is usually regarded as a disease of impaired differentiation or dedifferentiation. Differing from the traditional chemotherapeutic killing of normal cells, the differentiation therapy induces cancer cells to differentiate, altering their malignant biological behavior, preventing malignant proliferation, and transforming them into normal or near-normal cells to control cancer progression or even cure the patients. Compared with traditional surgery, chemotherapy, and radiotherapy, which are based on the idea that “cancer cells are irreversible,” differentiation induction gives a new option for cancer treatment. A representative drug is ATRA. Since 1980, Chinese medical scientists Zhen-Yi Wang and Zhu Chen successfully applied the oriental philosophy of “Dayu’s flood control” to the treatment of leukemia using ATRA to induce cancer cells to differentiate into normal hematopoietic cells. This milestone work in differentiation induction therapy established a brand new standard for

targeted cancer therapy. Based on their work on the effects and mechanisms of retinoic acid and its derivatives in cancer prevention and treatment, ATRA was used in treating APL, a completely new way to treat leukemia. The latest reports showed that the complete remission (CR) rates were 87%–92%, indicating its promising future in cancer treatment. APL is the first human malignancy that was cured with treatment targeted at a cancer-specific biological behavior. A characteristic non-random chromosomal translocation at t (15;17) occurs in 95% of APL patients. This translocation fuses the promyelocytic leukemia (PML) gene on chromosome 15 with the retinoic acid receptor α (RAR- α) gene on chromosome 17, leading to the expression of PML-RAR fusion protein, which is a key mechanism for the onset and differentiation blockage in APL. ATRA targets this locus, lifting the PML-RAR-mediated differentiation blockage, thereby inducing leukemic cells to differentiate into normal mature cells. Zhu Chen and Sai-juan Chen further discovered the pro-apoptotic and pro-differentiation role of ancient Chinese drug arsenic trioxide. Arsenic binds to cysteine residues in zinc fingers of PML-RAR α and PML, resulting in PML oligomerization, SUMOylation and degradation.

“Live with cancer” is made into reality with targeted therapy

Tumor progression is primarily driven by the activation of oncogenes. Thus, cancer progression can be delayed by suppressing this oncogenic drive. CML has a characteristic chromosomal abnormality called the Philadelphia chromosome (Ph⁺), which is present in 90% of CML patients. The Ph⁺ chromosome arises through a reciprocal translocation between the *abl* gene on chromosome 9 and the *bcr* gene on chromosome 22, resulting in a *bcr/ab1* fusion gene, and the expression of the *bcr/ab1* fusion protein, a tyrosine kinase. Imatinib mesylate (Gleevec), a tyrosine kinase inhibitor that selectively inhibits the *bcr/ab1* fusion protein, is the first recognized human tyrosine kinase inhibitor and has remarkable therapeutic effects on CML. The CR rate of naive Ph⁺ acute lymphocytic leukemia patients who had been treated with imatinib was as high as 95%. Imatinib is historically important because it provides evidence for the oncogene hypothesis. Following this strategy, inhibitors against various receptor tyrosine kinases have been developed, including inhibitors against epidermal growth factor receptor (EGFR), Her2, and platelet-derived growth factor receptor (PDGFR). Among these, the Her2-specific antibody, trastuzumab (Herceptin) is the most important because it further proves the importance of oncogenes in the onset and development of solid cancers. Her2/neu (erb-B-2) is overexpressed in 20%–30% of metastatic breast cancers and is associated with poor prognosis. When trastuzumab binds to the Her2 receptor, it blocks the corresponding receptor-mediated tyrosine kinase signaling pathway, inhibiting cancer growth and angiogenesis, which subsequently increases the susceptibility of cancer cells to apoptotic signals. Another possible mechanism for its action may be the antibody-dependent cellular cytotoxicity (ADCC) stimulated by the Her2-specific antibody. Trastuzumab used alone or in combination with chemotherapy can significantly suppress the progression of Her2-positive (++ to +++) breast cancer. Several studies regarding adjuvant therapy also confirm that trastuzumab can significantly reduce the recurrence and mortality rates of Her2-positive breast cancer patients. These new agents with more potency and less toxicity can potentially make cancer patients live a “normal” life despite tumors.

Simultaneous inhibition of cancerous “seeds and soil” enhances anticancer effects

A tumor does not live alone, that is, cancer cells (the “seeds”) have to get along with their stromal microenvironment (the “soil”) to survive as a tumor organ within cancer patients. Tumor stroma is composed of “normal” cells and their products. Stromal cells are relatively genetically stable, rarely develop drug resistance, and are ideal targets for anticancer therapy. Although Folkman first proposed to suppress cancer growth by inhibiting cancer angiogenesis in 1974, it was not until 1997 when endostatin, a specific anti-angiogenic agent, was discovered that the concept of anti-angiogenesis gained acceptance from the public. In 2004, bevacizumab, a vascular endothelial growth factor-specific monoclonal antibody, entered the market, indicating that anti-angiogenic theory has become reality. Clinical research has shown that anti-angiogenic therapy alone has a relatively weak anticancer effect, indicating that angiogenesis has a non-dominant role when compared with cancer cells. Based on the above theory, a strategy of simultaneous inhibition of both cancer cells and angiogenesis is developed. The anticancer effect of anti-angiogenic agents reflects the important role that the cancer stroma plays in cancer development and the intervention directed at the cancer stroma is an important supplement to the cancer cell-targeting strategy. Other cells in the cancer matrix or stroma, such as lymphocytes, macrophages, and fibroblasts, may also be targeted for cancer treatment in the near future.

“Antibody therapy” revives immunotherapeutic regiment in cancer targeting

The specific binding of an antibody to an antigen explains the high selectivity of antibody-based therapy. Rituximab is a CD20-specific antibody. Many clinical studies have confirmed that a combination of rituximab and chemotherapy significantly improves the prognosis in patients with diffuse large B-cell lymphoma and low-grade follicular lymphoma. CD20 is a lineage marker rather than an oncogene. The success of rituximab suggests that the monoclonal antibodies targeting lineage markers can also inhibit cancer growth via the immunological characteristics of antibodies such as ADCC and complement-dependent cytotoxicity. Antibody-mediated targeting strategy is also used in immunoradiotherapy and several radiolabeled antibodies have become available for the treatment of lymphoma, hepatic carcinoma, and lung cancer.

Challenges from bedside needs to bench investigation

Searching for specific and effective cancer targets

The major obstacle in developing effective targeted cancer therapy is differentiating distinct tumorigenic features from normal cellular physiological processes. The nature of tumor development remains a mystery; oncogenes and tumor suppressor genes control the onset and development of cancers, as well as participate in some essential physiological processes. Determining an appropriate level of interference with these genetic signals is a great challenge in oncology. The “cancer stem cell” hypothesis, proposed in recent years, has provided a new understanding of the mechanisms of the onset, development, and metastasis of malignant cancers. The vast majority of cells in most cancers are sensitive, to a certain degree, to traditional therapies such as radiotherapy and chemotherapy. However, a minor population of cancer cells carries an extremely strong capability of self-renewal, and even pumping out chemotherapeutic drugs extracellularly, which leads to drug resistance. These sub-groups of cells are named as cancer stem cells, cancer-initiating cells, or stem-like cancer cells. Investigations involving hematological malignancy first confirmed that the existence of cancer stem cells is responsible for the development of drug resistance, cancer recurrence, and metastasis, and stem cell transformation at various stages causes carcinogenesis. We have recently isolated some cancer cells from nasopharyngeal cancers with phenotypes similar to stem cells and demonstrated their greater capacity for radiation resistance, drug resistance, and metastasis than other cancer cells. Are these cells with phenotypes similar to stem cells actually a manifestation of cancer heterogeneity? As we know, genomic instability is one of the hallmarks of cancer cells and it leads to extreme heterogeneity in cancer cells. This is why we often observe marked changes in chromosome number, as well as frequent chromosome fragment deletions or amplifications in cancer cells under microscopic examination. These changes seem to appear without any discernable pattern. Therefore, we need to develop drugs that more specifically target the cancer cells with stem cell phenotypes and be more cautious in the use of cytotoxic chemotherapeutic drugs that may induce genomic instability.

Individualized therapy guided by molecular markers to increase therapeutic efficacy

Malignant tumors, as a particular type of disease, have marked heterogeneity at the molecular level and their genomic instability leads to unpredictable tumor progression. Evidence-based medicine presently tends to neglect the heterogeneity of cancer cells, and instead, guide individual treatment with generalized clinical outcome data. This practice may be very misleading and can cause targeted cancer therapy to be undervalued significantly. With chip technology and bioinformatics techniques, precisely classifying cancer cells is possible at the structural and expression levels of genes (molecular classification), which can be used to guide treatment. For this purpose, some preliminary studies have been conducted at the Sun Yat-sen University Cancer Center. The development of tumors is a multi-gene and a multi-step process, therefore, simultaneous or sequential multi-targeted therapy is required to achieve the goal of “living with cancer.” If we are able to define the abnormal genetic signal(s) within the entire genome that a cancer is dependent on at certain stages of cancer development, then precisely targeted therapy is possible. Subsequently, considering cancer heterogeneity, the strategy can be summarized as “same disease, different treatments.” For targeted therapy, maximizing the pharmacological effects of molecular targeted agents is essential to improving therapeutic accuracy. These drugs are non-cytotoxic with prominent individual differences in tolerance and drug concentrations among patients. The optimal effective dose within the range of the minimal effective dose and the maximal tolerable dose through traditional clinical tests is difficult to determine. Thus, the

treatment should be titrated individually according to the target-specific biomarkers during therapy to achieve optimal pharmacotherapy of the molecular targeted agents.

Chinese contributions to targeted cancer therapy

Accumulating evidence has supported targeted cancer therapy as a promising new therapeutic strategy. The treatment of malignant cancers is undergoing a transition from a change of quantity to a change of quality. For chemotherapy-sensitive cancers, the combination of targeted cancer therapy with traditional therapies improves the prognosis. For chemotherapy-insensitive cancers, targeted cancer therapy will gradually replace traditional therapies and eventually evolve towards the “post-chemotherapy era” in the near future. We are very proud to see that, during this remarkable evolution, Chinese scientists have made significant contributions. Zhen-Yi Wang and Zhu Chen discovered the internationally recognized phenomenon of ATRA-induced differentiation in leukemic cells. Zhu Chen and Sai-juan Chen further revolutionized ancient Chinese “poison” arsenic trioxide in leukemia treatment. Yong-Zhang Luo developed Endostar, a modified version of human endostatin. Zhi-Nan Chen developed radiolabeled monoclonal antibodies for the immunoradiotherapy of hepatic carcinoma. Chao-Hui Peng started the mass production of the first gene therapy product, recombinant human p53 adenovirus injection. We are fortunate to practice medicine in the era of translational medicine to witness the power of targeted cancer therapy in malignancy treatment.