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Research Progress of Genome-Guided Precision Oncology Technology

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Abstract: *As the diagnosis and treatment of diseases including cancer have entered a new era thanks to the molecular and cellular biology, especially related omics research progress since the 21st century, the so-called precision medicine that tailors diagnosis, prognosis, and treatment strategy for the actual needs of different patients based on clinicopathological features combined with molecular expression profile features has emerged. Precision medicine will change the one-size-fits-all model for groups from traditional medicine to help reduce the incidence of misdiagnosis, mistreatment, and over-treatment and improve curative effects. Genome-guided oncology refers to a new therapeutic idea for drug use based on tumor gene characteristics beyond histological disease classification and pathological classification. The relevant new drug development technology and new method of clinical trial design based on this idea provide a new thought to precision oncology. The paper summarizes the research progress of genome-guided precision oncology technology.*

Keywords: *Genome-guided; Oncotherapy; New Technology*

1. Introduction

How to treat tumors more effectively? Generally, experts from medical oncology, radiation oncology, and pathology and professionals from multidisciplinary oncology institutes targeted different organs with tumors discuss a patient's physical condition and treatment options and then synthesize relevant opinions of specialists from corresponding oncology departments such as abdominal oncology surgery, gastroenterology, gynecology, and urology to give treatment strategies and nursing plans for traditional cancer. Moreover, the final recommendation is based on the patient's medical history, viable treatment options, and evidence-based medicine. [1]However, traditional methods and strategies have choked off cancer diagnosis and treatment and may cause side effects.

Precision oncology refers to tailoring diagnosis, prognosis, and treatment strategies for the actual needs of different patients combining genetic technology, biotechnology, and imaging technology based on a patient's physical condition and clinical data. Oncology technologies include customization of the individual scheme based on molecular typing, molecular targeting treatment and its prediction and monitoring of therapeutic response and resistance, precision surgery, and physiotherapy.[2] In recent years, with the development of precision medicine, precision oncology based on precision treatment aims to identify patient populations with a common biological basis, choose drugs or treatment methods that are most likely to benefit patients, and understand tumor characteristics for clinical decisions at the molecular level, thus improving diagnosis and treatment.

2. Current status of tumor precision medicine

2.1 Combination of oncotherapy and gene technology

As a genetic disease, a tumor belongs to a genetic disorder caused by some influence.[3] Therefore, all tumor diseases regardless of triggers can be explained by genetic mutation. The new progress in human gene technology provides technical support for developing tumor precision medicine. For example, the latest gene measurement technology can express and test genes more precisely, thus providing new technical assistance for tumor precision treatment. As detection technology advances and testing cost decreases, researchers have begun to test a single gene cell with a single-cell level accuracy from the individual level. As it were, tumor precision treatment will be higher in accuracy. [4]

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2.2 Combination of oncotherapy and omics technology

A tumor caused by genetic mutation is a complex and special disease, which means genomics alone cannot accurately analyze the causes of the tumor and cure methods, so the comprehensive omics technology comes in handy. The types of genetic mutation associated with tumors include point mutations, base mutations, chromosome reversals, and others. Besides, the methylation of genes and changes in chromosome non-histone may trigger a tumor. Therefore, it is necessary to master various omics technologies to complete the research on the causes and treatment of tumors. The latest omics technologies related to tumor precision medicine include genomics, proteomics, immunomics, genomics, and glycomics.

2.3 Combination of oncotherapy and big data technology

Data is the premise for the development of medicinal technology and also the foundation for oncotherapy.[5] Especially in oncology precision medicine, big data is indispensable. Establishing relevant data information including large samples and exploring tumor diseases and genetic databases by using the rich data in today's big databases are necessary for studying tumor precision medicine. A large amount of data is conducive to a random sampling survey of samples and mastering some rules and causes of genetic changes and tumor generation through comprehensive analysis. With the updating and improvement of large databases, an individual-centered full-coverage database has been set up based on the tumor precision medicine database, thus helping know the relationship between tumors and drugs and explore the causes and treatment methods of tumors through the interpretation of basic data.

3. The development of gene sequencing technology has promoted the application of precision oncology

3.1 Upgrading of gene sequencing technology

Identifying oncogene and tumor suppressor genes provides the basis for different cancer gene types. The fast-growing gene sequencing technology facilitates the discovery of molecular characterization of tumors that plays a critical role in the application of precision oncology as a biomarker for predicting anticancer drug susceptibility or resistance. As the first-generation DNA sequencing technology dideoxy chain-termination method, or sanger method,[6] the second-generation modern massively parallel sequencing, or next-generation sequencing (NGS)[7], and the third-generation single-molecular real-time sequencing[8], next-next-generation sequencing come out in succession, the sequencing read length changed from long to short, and the long read sequencing technologies are also improved. At the same time, the corresponding throughput changed from low to high, with lower costs from 10 million dollars to less than 1,000 dollars[9]. It is not far off that everyone can afford the sequencing cost.

3.2 Expandable gene targeted therapy for different tumor types

It is common to use second-generation sequencing technology to evaluate a wide range of molecular changes. By the analysis of NGS, learning that NGS is sensitive to detect specific molecular changes and detection may eventually lead to accompanying changes in resistance to specific targeted drugs. Research results of large-scale sequencing have shown that most of the genome changes currently targeted in specific tumor therapies are also present in other tumor types, like BRAF(V600E) gene mutation,[10] which provides a basis for the expansion of gene targeting therapy for different tumor types in the future. A third of BRAF(V600E) mutations are commonly seen in melanoma, thus developing four RAF and MEK inhibitors and two-thirds of BRAF(V600E) mutations present in other tumor types, such as thyroid cancer, and non-small cell lung cancer, suggesting the extended applicability of RAF and MEK inhibitors as shown by the current detection data.[11]

3.3 Circulating tumor DNA detection

Circulating tumor DNA (ctDNA) detection is used to obtain the characteristics of the tumor genome from the blood through sequencing technologies, which is suitable for detecting hard-to-diagnose tumor types without typical symptoms and specificity after detection. This method avoids invasive biopsies for confirming the diagnosis and may revolutionize the diagnosis, prognosis, and treatment decisions of different tumor types based on histology.

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4. A new field of drug development guided by the concept of precision oncology

4.1 Sub-type and mutant type selective inhibitors

According to the *Toward a More Precise Future for Oncology*, Sub-type and mutant-type selective inhibitors are used for tumor precision treatment to improve the curative effect and tolerance of drugs (as shown in Figure 1). For instance, in early years, the targeted therapy with pan-PI3K inhibitor has limited efficacy for the PI3K pathway, one of the most common mutations in cancer; PI3K sub-type selective inhibitor has a greater efficacy compared to pan-PI3K inhibitor and PI3K/mTOR dual inhibitor. In addition, sub-type specific inhibitors can also minimize drug toxicity.

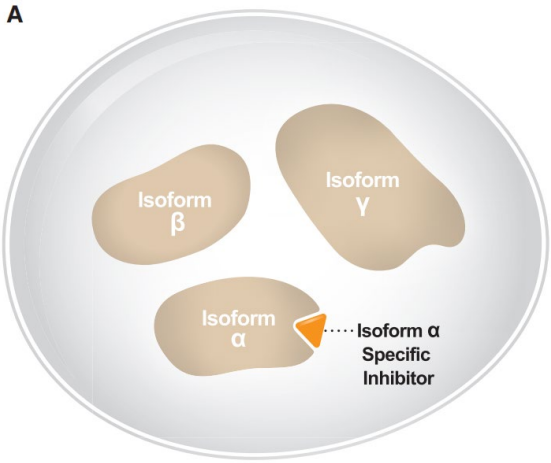

Figure1. Isoform-selective inhibitors bind to an individual protein isoform within the cell.[12]

In recent years, drug selectivity has gone beyond sub-type selectivity towards the direction of the single mutant allele. This kind of selectivity inhibits cancer-causing proteins and retains wild-type proteins in mutations. As one of the most common cancer-causing mutant genes in cancer, KRAS has long been seen as a non-drug target partly because of a lack of binding pockets. However, recent improvements in small molecule design have facilitated the development of high-selective inhibitors, which can form irreversible covalent bonds by reacting with mutant cysteine of KRASG12C and lock proteins in an inactive GDP binding state. In the absence of this mutant cysteine, inhibitors will not react with wild-type KRAS. Early results from the Phase I clinical trial of KRASG12C inhibitors have shown that inhibitors have minimal toxicity to NSCLC patients with KRASG12C mutation.

4.2 Antibody-drug conjugates (ADC)

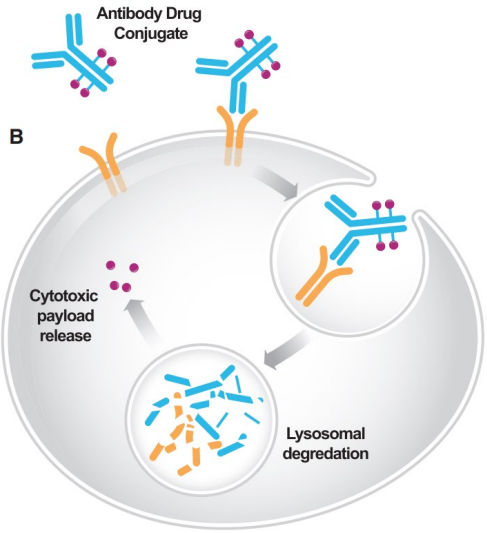

Figure 2. Antibody-drug conjugates bind to cell-surface antigens and are internalized into the cell where they release a cytotoxic payload to induce cell death.

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By linking cytotoxic drugs directly to targeted antibodies, ADCs are used to expand the therapeutic window for conventional cytotoxic drugs (As shown in Figure 2). However, ADCs have more toxicity than expected because of the expression of normal cell targets in host tissues, nonspecific cleavage of toxins, and other unknown mechanisms. Such drugs have entered the clinical trial after continuous improvement. Formed by the coupling reaction of trastuzumab and deruxtecan, a cytotoxic topoisomerase I inhibitor, the ADC drug trastuzumab-deruxtecan (DS8201) has shown unprecedented activity in HER2-driven cancers, including breast and stomach cancers with high HER2 expression. The key to developing ADCs is to determine the best tumor-specific targets and optimize drug safety.

4.3 Proteolysis targeting chimeric molecule (protacs)

Such new therapies for oncology precision treatment as PROTACS and molecular glue based on protein degradants generally involve the use of bi-functional molecules that bring targets close to ubiquitin ligase and eventually lead to target degradation (As shown in Figure 3). Currently, the application of this technology in cancer treatment is still in its infancy. Many key drivers of cancer, including transcription factors, cannot be targeted by current therapies because these drivers are not expressed on the surface of cells, which makes antibodies inaccessible, or lack a binding pocket to which small molecule inhibitors can attach. PROTACS may overcome these challenges: simultaneously binding to target proteins and E3 ubiquitin ligase, and promoting target protein degradation based on the mechanism of endogenous protein degradation in cells.[13] ARV-110 is the first such drug to enter phase I clinical trial, linking E3 ubiquitin ligase to androgen receptors(NCT03888612) in prostate cancer patients. This new method for reducing protein levels in cells may allow previously non-drug targets to become effective targets.

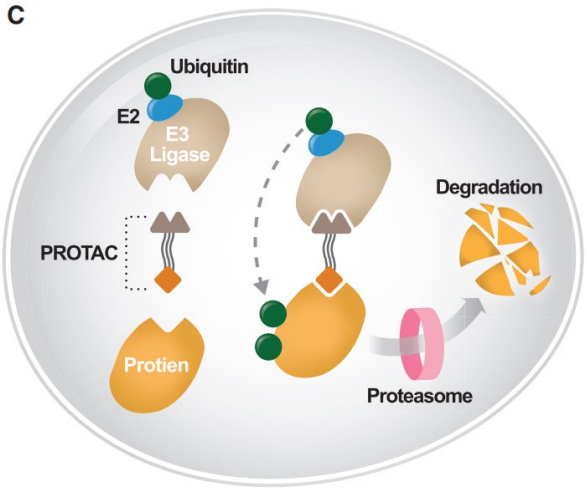

Figure 3. Proteolysis-targeting chimeras (PROTACs) bind both mutant proteins and E3 ubiquitin ligase, facilitating proteasomal degradation of the target.[12]

4.4 Protein-refolding small molecules（Protein Refolders）

Now specialists are developing protein-refolding small molecule drugs that restore proteins' lost activity by reshaping their conformation, thereby restoring the natural function of mutant proteins (as shown in Figure 4). It is proven that this method can treat cystic fibrosis. As a non-neoplastic genetic disease, cystic fibrosis is characterized by the production of lots of mucus due to mutations in the gene encoding the cystic fibrosis transmembrane conduction regulatory protein (CFTR). Protein refolding small molecules reduces the clinical sequelae of cystic fibrosis by allowing CFTR to re-reach the cell surface and to make a play like wild-type proteins. Although we are exploring the application of protein refolding small molecules in cancer, it represents a novel approach to targeting mutant tumor inhibitors. Loss-of-function mutation in the tumor inhibitor TP53 is the most common mutation in cancer. However, treatments specifically for cancers with TP53 mutation have not been approved. We are currently developing small molecules that restore the activity of mutant TP53 by protein refolding, which provides the added benefit of mutation-specificity, thereby reducing toxicity in addition to increasing the number of possible drug targets.

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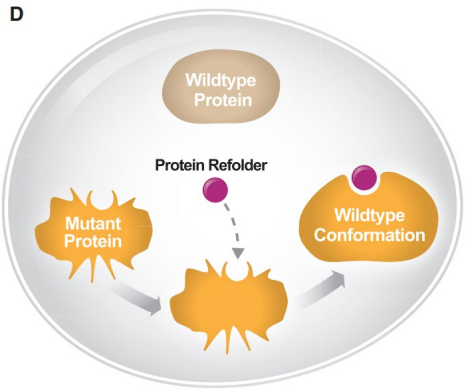

Figure 4. Protein refolders enable mutant proteins to regain wild-type conformation and activity.

4.5 Drugs of natural origin

4.5.1 Natural products are abundant, but the total number of new approved drugs remains low

Natural products refer to active substances extracted from organisms of natural origin, such as chemical composition and metabolites from plants, animals, microorganisms, and marine organisms, which are helpful to screen for anti-tumor targeting drugs of natural origin. NEWMAN D. J. and other scholars have found by retrieving literature from 1981 to 2014 that a total of 174 compounds of natural origin with anti-cancer activity have been discovered.[14] Although new compounds of natural origin are continuously being discovered in recent years and many of them have been approved for clinical treatment or clinical trials, such compounds have a small total number and their potential tumor-targeting activities need to be discovered. Take, for example, a 2019 study published in Science: phosphatase and tensin homology deleted on chromosome ten (PTEN) missing from human chromosome 10, tumor suppressor gene can pass PI3K-Akt signaling pathway, thereby inhibiting tumors produce and develop while the over-expression of HECT type E3 ubiquitin ligase can lead to PTEN inactivation. In vivo experiments, indole-3-carbinol (I3C) was extracted from broccoli by researchers and confirmed to inhibit WWP1 expression, thereby restoring PTEN activity.[15]

4.5.2 A database for natural products provides a information source for screening new drugs of natural origin

KRUSHKAL J and other scholars have selected 1302 natural products, and their derivative small molecular structures such as paclitaxel, camptothecin, and their derivatives, colchicine and its derivatives, and centaureidin in Natural Products Resource Library of National Cancer Institute in America and reacted them with molecular characteristics of NCI-60 cancer cell line panel (NCI-60) genome in vitro

for an association study, finding that mutations in multiple gene expressions including DNA damage repair for SLFN11, CYP2J2, EPHX1, GPC1, ELF3, MGMT, members of the NOTCH family, ATP binding cassette (ABC), solute carrier (SLC) transporters, tyrosine kinase, and BRAF (V600E) are associated with the reaction of NCI-60 to specific classes of natural products.[16]

4.5.3 Traditional Chinese medicine provides rich materials for developing tumor-targeting drugs of natural origin

Traditional Chinese medicine (TCM) is an important part of drugs of natural origin. The effective components extracted from TCM can regulate tumors through multiple targets. Liu J and other scholars have contrasted the effects of 166 compounds to 420 anti-tumor or immune-related genes in 47 TCM with supporting or anti-pathogenic effects by high-throughput sequencing and high-throughput screening strategy (HTS2) combined with network pharmacology, finding that predicted targets of 2 TCM compounds were enriched in anti-tumor-related pathways and the overall inhibitory effect of compounds extracted from TCM with anti-pathogenic effect on tumor cell proliferation was significantly higher than that of TCM with supporting effect. For example, galloylpaeoniflorin, white peony root extract, can affect gene expression in the MAPK signaling pathway, and the two compounds, acetyl ursolic acid and specnuezhenide in glossy privet can up-regulate the gene expression in T cell signaling expression. In recent years, studies about tumor-targeting therapy with TCM components. For example, berberine as a photosensitizer combining with photodynamic therapy (PDT) has a significant anti-cancer effect on renal cell carcinoma, triggering the differential expression of 3 target genes (FIGF, TERT low expression, PLK3 over-expression). Besides, triptolide can inhibit the growth of nasopharyngeal cancer cells in vitro

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and in vivo by interfering with NC -THOR-IGF2BP1 signaling pathway; brucine inhibits the growth of glioblastoma cells by decreasing the expression of c-Myb proto-oncogene; curcumin promotes the expression of miR-152-3p by inhibiting the ERK/ NF-κB signaling pathway, allowing the inactivation of the c-METPI3K Akt signaling pathway to delay the progression of melanoma.[17]

5. Conclusion

As the scope of precision oncology is rapidly expanding, more and more patients will benefit from this therapy. In this context, the author suggests further improving drug development and optimizing drug use and clinical trial design, thus bringing more benefits to patients. In the future, key development directions for precision oncology include: (I) Establishing an information-supporting system: it includes a bio-bank, bio-information database, and bio-information repository, which can be established by exploring and integrating clinical information related to tumor precision therapy and biological big data. (II) The accurate early-warning and diagnosis system of tumors: it includes molecular diagnostic, and liquid biopsy of tumors, molecular imaging and molecular pathology diagnosis, early-warning and early-diagnosis technology system, and kit development. (III)The accurate classification and prediction of tumors: it includes molecular classification/staging of tumors, prediction of prognosis and metastasis recurrence, and monitoring therapeutic response and drug resistance.

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