INVITED REVIEW

Translational progress on tumor biomarkers
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Abstract
There is an urgent need to apply basic research achievements to the clinic. In particular, mechanistic studies should be developed by bench researchers, depending upon clinical demands, in order to improve the survival and quality of life of cancer patients. To date, translational medicine has been addressed in cancer biology, particularly in the identification and characterization of novel tumor biomarkers. This review focuses on the recent achievements and clinical application prospects in tumor biomarkers based on translational medicine.

Introduction
For decades, research on life science has made major breakthroughs, including the discovery of stem cells and completion of human genome sequencing, which have great significance in the promotion of medical research progress. However, few basic research findings have actually been applied to clinics for the benefit of patients. A new model of research, translational medicine, has been introduced to fill the gap between basic research and clinical application.1–3 It is a two-way, open circulation research system, from bench to bedside and from bedside to bench.4,5 The translational medicine research model has become a strategy direction for the field of biomedical research.

Translational medicine plays an important role in the research of malignant tumors and clinical treatment.6 Malignant tumors have become the leading cause of death in the Chinese population. Although basic research on tumor biology has broadened our understanding of factors such as occurrence, metastasis, and drug resistance, care of cancer patients is generally by indiscriminate treatment, that is, patients are given the same treatment without fully considering their individual biological characteristics; thus, the general survival rate has not significantly improved in the last 20 years.7 Tumor biomarkers are of potential use in early cancer diagnosis, anticancer therapy development, and monitoring the response to treatment. We provide a mini-review of recent advances in tumor biomarkers based on translational medicine.

Research development and clinical application of tumor biomarkers

Concepts of tumor biomarkers
Tumor biomarkers are substances present in or produced by a tumor itself or by the host microenvironment in response to the process of tumorigenesis and progression. They cover a
broad range of biochemical entities, such as proteins, hormones, enzymes, and oncogene products. These substances can be found in cells, tissues, or body fluids, and can be qualitatively or quantitatively detected by chemical, immunological, and molecular biological techniques. Tumor biomarkers represent an effective tool for tumor diagnosis, treatment, prognosis, and therapeutic monitoring. The Early Detection Research Network (EDRN) is a large network project in translational research sponsored by the United States National Cancer Institute (NCI). This project mainly focuses on early tumor diagnosis, metastasis and relapse detection, prognosis, and targeted therapy.

Tumor biomarkers in clinical application

As a key to individual medical treatment, research on tumor biomarkers has increasingly gained attention. However, the clinical application of tumor biomarkers is somewhat limited. To date, only 20 types of tumor biomarkers have been used in the clinical setting. Some of these markers are confined to a certain type of cancer, while others exist in two or more types of tumors; however, there is no “universal” tumor marker present in all types of cancer. According to the chemical nature of tumor markers, they can be divided into six types: oncofetal antigens (carcino-embryonic antigens [CEA], alpha fetoprotein [AFP]), carbohydrate antigens (CA125, CA15.3, etc.), enzymes (prostate-specific, neuron specific enolase, etc.), hormones (human chorionic gonadotropin, calcitonin, etc.), proteins (ceruloplasmin, etc.) and genes (P53, V-KI-ras2 Kirsten rat sarcoma viral oncogene homolog [KRAS], etc.). Tumor biomarkers commonly used in the clinical setting are summarized in Table 1.

Latest progress of molecular biomarkers of tumors

Tumor screening and early diagnosis

Conventional tumor biomarkers include tumor antigens and differentially expressed gene products, such as breast cancer 1, early onset (BRCA1) and BRCA2. Researchers from Peking University recently reported that the reproducibility of cancer-specific copy number variation (CNV) offers potential for noninvasive circulating tumor cell (CTC)-based cancer diagnostics. Kinde et al. performed whole genome sequencing on cervical secretions for ovarian and endometrial cancer diagnosis, and established suitable routine screening methods for these tumors. Wang et al. suggested that Hsp90a is a potential tumor biomarker. Recent discoveries have shown that micro ribonucleic acid (miRNA) is stable in serum and can enter peripheral circulation; thus, circulating miRNA may be used as a biological tumor marker for early diagnosis. Harris et al. reported that miR-375 expression level was closely related to the death rate of patients with head and neck cancer, and can, thus, be regarded as a novel tumor biomarker. In 2014, Ribeiro et al. proposed that miR-125b might serve as a predictive biomarker for the occurrence of cervical cancer and that MiR-34a might be regarded as a potential biomarker for further development. Kelber et al. reported that pseudopodium-enriched atypical kinase 1 (PEAK1) was a novel biomarker for the early prediction of pancreatic cancer. These findings are expected to be applied to early diagnosis and screening if results from a large number of clinical specimens can be validated.

Table 1 Summary of commonly used tumor biomarkers

| Molecular markers | Types of tumors |
|-------------------|-----------------|
| AFP               | Hepatocellular carcinoma, germ cell tumors |
| ALK               | Non-small cell lung cancer, anaplastic large cell lymphoma |
| B2M               | Multiple myeloma, chronic lymphocytic leukemia |
| BCR-ABL           | Chronic myelogenous leukemia |
| BRAF mutation V600E | Cutaneous melanoma, colorectal cancer |
| β-HCG             | Choriocarcinoma, testicular cancer |
| CA125, HE4, ROMA, OVA | Ovarian cancer |
| CA15.3, CA549, MCA | Breast cancer |
| CA27.29, Her-2/neu, ER/PR, uPA, PAI-1, 21-Gene signature, 70-Gene signature | colorectal cancer |
| CA19-5            | Pancreatic cancer, gallbladder cancer, bile duct cancer, gastric cancer |
| CA19-9, CA50      | Gastrointestinal tract cancer, pancreatic cancer |
| CA242             | Gastric cancer, pancreatic cancer |
| CA72-4            | Medullary thyroid carcinoma |
| Calcitonin        | Breast cancer, pancreatic cancer |
| CEA               | colorectal cancer |
| CD20              | Non-Hodgkin lymphoma |
| CgA               | Neuroendocrine tumor |
| DU-PAN-2          | Pancreatic cancer, endometrial cancer |
| EGFR, CYFRA 21-1  | Non-small cell lung cancer |
| FDP, NMP22, Chromosomes 3, 7, 17, and 9p21 | Bladder cancer |
| HAb18G/CD147      | Hepatocellular carcinoma |
| IPO-38            | Gastric cancer |
| KIT               | Gastrointestinal stromal tumor, mucosal melanoma |
| KRAS              | Colon cancer, non-small cell lung cancer |
| Lactate dehydrogenase | Germ cell tumor |
| PSA, PAF, PCA3    | Prostate cancer |
| Thyroglobulin, galectin-3 | Thyroid cancer |
Tumor deterioration biomarkers: Metastasis, recurrence, and drug resistance

Metastasis is one of the primary causes of death in cancer patients. When tumor metastasis occurs, the routine clinical treatment outcome is poor, resulting in high mortality; however, when a tumor is diagnosed, many patients face overtreatment with feasible side effects because there is no optional way to determine whether there is a metastasis. According to statistics, 20–25% of patients diagnosed with lymph node-negative breast cancer will experience tumor metastasis in the 10 years after surgery, but as many as 90% of patients receive postoperative systemic chemotherapy. It is very important to learn how we can more accurately determine the probability of tumor metastasis, and choose relevant treatments with fewer side effects. Early diagnosis of tumors can help patients receive timely and effective treatment. Early diagnosis and prediction of tumor metastasis can also provide more detailed and reliable tumor information for doctors. It may help doctors to decide whether further systemic treatment is needed and choose appropriate clinical treatment after primary tumor resection, in order to improve patients’ quality of life and prolong survival.

Some tumor biomarkers may become better predictors of tumor recurrence and metastasis because their abnormal expression often occurs earlier than other detection signs, such as clinical imaging or symptoms. They may also be used to predict the tumor response to different treatments and evaluate prognosis. Dynamic monitoring serum AFP after hepatocellular carcinoma surgery and CEA after colorectal cancer can be adopted for early diagnosis of recurrence and metastasis. Chen et al. reported that serum cholinergic muscarinic 2 receptor (CHRM2), family with sequence similarity 5, member C (FAM5C), and promoter hypermethylation of myosin light chain kinase (MYLK) were considered gastric cancer markers, because their serum levels significantly decreased after tumor resection; these findings can be used to evaluate the effect of surgery and prognosis. Dynamic monitoring serum AFP after hepatocellular carcinoma surgery and CEA after colorectal cancer can be adopted for early diagnosis of recurrence and metastasis. Chen et al. reported that serum cholinergic muscarinic 2 receptor (CHRM2), family with sequence similarity 5, member C (FAM5C), and promoter hypermethylation of myosin light chain kinase (MYLK) were considered gastric cancer markers, because their serum levels significantly decreased after tumor resection; these findings can be used to evaluate the effect of surgery and prognosis. Recently, Tsai et al. observed that a higher serum level of miR-196 correlated with the recurrence of gastric cancer in gastric cancer patients. Budhu et al. found that the expression of a 20-miRNA signature had important significance for identifying hepatocellular carcinoma patients who are likely to develop metastases and recurrence. Lu et al. also reported that a rise in chemokine CCL2 level might be an important indicator for bone metastasis in prostate and lung cancers.

Tumor prognostic biomarkers

The application of molecular markers means that tumor prognosis assessment is no longer confined to clinical pathological parameters. Markers can more accurately assess prognosis by classifying molecular signatures. Mahmoud et al. observed that the number of breast tumor-infiltrating CD8+ T lymphocytes was positively correlated with survival period; therefore, it can be considered as an evaluation indicator for the prognosis of breast cancer patients. Winter et al. found that pancreatic cancer patients with higher expressions of signal transducer activator of transcription 3 (STAT3), FBJ murine osteosarcoma viral oncogene homolog (FOS), and jun proto-oncogene (JUN) have relatively shorter survival periods. Those with a higher expression of specificity protein 1 (SP1), causal-type homeobox transcription factor 2 (CDX2), CCAAT/enhancer binding protein alpha (CEBPA) and BRCA1 have relatively longer survival periods. Therefore, these seven genes combined with pathological parameters can accurately classify patients into good and poor prognosis groups, and help to determine whether adjuvant therapy is needed. Lee et al. selected 27 proteins related to the prognosis of gastric cancer from 56 genes, based on which patients were divided into two types. Type I tended to be intestinal and early, with a better prognosis than type II; the prognostic accuracy reached 73% or more. Moreira et al. reported that neuronal PAS domain protein 3 (NPAS3) drives the progression of human malignant astrocytomas as a tumor suppressor and is a negative prognostic marker for survival. A unique metastatic gene signature enables prediction of tumor relapse in early stage hepatocellular carcinoma patients.

Viral-derived biomarkers of tumor

In recent years, virus-derived DNA, messenger (m)RNA, and proteins, as biomarkers for virus-associated tumors, have been widely used in different clinical applications in the management of tumors, including screening, monitoring, and prognostication. Therefore, the analysis of virus-derived DNA, mRNA and proteins is expected to become an important tool in the management of cancer in the near future.

Epstein-Barr virus (EBV) infection is an important etiology for nasopharyngeal carcinoma (NPC), as the EBV genome can be detected in almost all NPC tumor tissues. Plasma EBV-DNA, when quantitatively analyzed using real-time polymerase chain reaction, has been developed as a biomarker for NPC. In addition, as a result of excellent sensitivity and specificity, plasma EBV-DNA can also be used as a non-invasive biomarker for EBV-positive Hodgkin’s lymphoma; serial monitoring could predict response to therapy. Recent research has indicated that autoantibody signatures combined with EBV capsid antigen-IgA (VCA-IgA), as a biomarker panel of NPC, might aid in the screening and diagnosis of NPC. Nishino et al. revealed that a high serum level of Epstein-Barr virus–induced gene 3 (EBI3), as an independent prognostic factor, was associated with a poor lung cancer prognosis, suggesting that EBI3 is a potential serum and tissue biomarker, as well as a therapeutic target for lung cancer. Epidemiological studies have emphasized that the
human papillomavirus (HPV) is the main etiological factor for cervical cancer and DNA of specific HPV types has been found in almost all cervical cancer biopsies.85–89 attributed to its highly sensitivity, accuracy, and reliability, HPV DNA testing has become a powerful screening tool for the secondary prevention of cervical cancer.86–89 In addition to high-risk HPV-DNA, the constitutive expression of the viral oncogenes E6 and E7 is another characteristic of cervical cancer.90 Dürst et al demonstrated that HPV-E6-E7-mRNA could be used as a molecular marker for disseminated cervical cancer in order to predict the risk of recurrence.91 Moreover, compared with the HPV-DNA test, RNA-based HPV assay was more specific and sensitive for the detection of high-grade pre-cancerous lesions and may be used in primary cervical screening for women 30 years and older.92

Tumor biomarkers for targeted therapy

The intervention of some tumor related genes was observed to achieve anti-tumor effects. This so-called “targeted therapy” provides a new method for tumor management. Molecules for targeted therapy can be divided into the following categories: oncogenes and tumor suppressor genes (c-Ras and p53), epidermal growth factor receptor (EGFR), the key protein kinase of signal transduction (PI3K), nuclear transcription factor κB (NF-κB), transmethylase or histone deacetylase (HDAC), and tumor angiogenesis related molecules.93,94 Targeted therapeutic options include small molecular compounds, antibodies, recombinant virus vectors and small interfering (si)RNAs. For example, the monoclonal antibody trastuzumab interferes with human epidermal growth factor 2 (HER2)/neu over-expression in breast cancer; the small molecule inhibitor imatinib is used for break point cluster/Abelson (BCR/ABL) gene rearrangement in chronic myeloid leukemia, caused by chromosomal translocations; the small molecule inhibitor erlotinib for EGFR-mutated lung cancer; and promyelocytic leukemia (PML)-retinoic acid receptor (RAR) alpha, a fusion protein containing sequences from the PML zinc finger protein and RAR alpha, as a direct drug target in arsenic treatment for acute PML.95

Cho-Park and Stellar recently reported an adipose-ribosyl transferase, tankyrase (TNKS), could promote 26S proteasome activity, and a small molecule inhibitor, XAV939, could inhibit TNKS activity and block proteasome activity, which suggests that a small molecule could be used in the treatment of multiple myeloma.96 Emerling et al. showed that a subset of breast cancers express higher levels of the type 2 phosphatidylinositol-5-phosphate 4-kinases α and/or β (P15P4Kα and β) and provided evidence that these kinases are essential for growth in the absence of p53. They also indicated that inhibitors of P15P4Ks could be effective in preventing or treating cancers with mutations in p53.97 Leprivier et al. discovered a protein, eEF2K, which is not important in normal cells but essential in cancer cells; thus, blocking the function of eukaryotic elongation factor-2 kinase (eEF2K) can effectively kill cancer cells without affecting the biological process of normal cells. Therefore, blocking the protein is expected to be significant in the treatment of cancer.98

Clinical application prospects of tumor biomarkers

Research on molecular markers of tumors has made great progress in recent years. Tumor biomarkers with potential diagnostic and therapeutic value are accumulating. However, it is important to direct cancer research on diagnosis and treatment toward applying these fundamental research findings to the clinic as soon as possible, and applying novel tumor molecular markers to early diagnosis, targeted therapy, and individualized treatment. Excessive medical treatment should be avoided through the analysis of new tumor biomarkers and appropriate treatments. A large database of clinical specimens to validate new tumor biomarkers is required; therefore, a worldwide EDRN system should be established and a series of standards in the process from tumor biomarker discovery to clinical application should be set.

Conclusion

Translational research on tumor biomarkers has successfully promoted the development of tumor treatment and has brought new hope for cancer patients. As the concept of translational medicine is carried into the field of clinical medicine and basic research, particular emphasis needs to be directed to clinical application, which, in turn, will provide feedback to researchers in order to improve solutions and serve patients.

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Disclosure

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Recent advances in tumor biomarkers

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