Research progress and clinical application of tumor markers in medical laboratory science

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Abstract

In recent years, the incidence of cancer has risen steadily, seriously endangering people's lives and health, and has gradually become the main cause of human death. China's cancer prevention and treatment policy is "early detection, early diagnosis and early treatment." Therefore, the long-term search for tumor markers (TM) for early diagnosis has become the focus of attention. This article mainly describes the classification of tumor markers and its related research progress and clinical application.

Keywords

Research progress, application, medical laboratory science.

1. Introduction

The latest report from the World Health Organization (WHO) shows that in the next 20 years, the number of cancer cases per year in the world will rise from 14 million in 2012 to 22 million, and the number of deaths will increase from 8.2 million per year to 13 million per year. [1]. At present, the work of cancer prevention and treatment has made some progress, and the 5-year survival rate of patients with malignant tumors has improved. However, there are still great difficulties in the early diagnosis and localization of tumors, which makes most patients diagnosed at an advanced stage and missed the best time. The curative effect is poor [2]. Therefore, in the diagnosis and treatment of tumors, early detection, early diagnosis and early treatment directly affect the prognosis and survival of patients, which is an effective means to improve the diagnosis and treatment of malignant tumors, reduce their mortality and improve the prognosis of patients [3-4].

2. Overview of tumor markers

Tumor is a disorder in which the body of a local tissue loses its normal regulation at the gene level under the action of various carcinogenic factors, resulting in abnormal clonal hyperplasia. The tumor marker (TM) refers to a substance that changes abnormally during the occurrence and proliferation of malignant tumors due to the expression of related genes of tumor cells or the body's response to tumors. It is present in body fluids, tissues or cells [5].

According to clinical evaluation criteria, tumor markers should have the following characteristics: 1) It must be produced by malignant tumor cells, and can be detected in blood, tissue fluid, secretion fluid or tumor tissue; 2) It is lower in normal tissues or benign tumors 3) The tumor marker of a tumor should be detectable in most patients with the tumor; 4) It can be detected before clinically no clear evidence of tumor diagnosis; 5) The amount of tumor markers is best Reflect the size of the tumor; 6) To a certain extent, it can help to estimate the treatment effect, predict tumor recurrence and metastasis [6].

The ideal tumor marker should have the following characteristics: 1) Having high sensitivity, early detection and early diagnosis of tumor; 2) Having good specificity, only tumor patients are positive, it can distinguish differential diagnosis of benign and malignant tumors; 3) It can locate tumors, have organs Specificity; 4) It is related to the severity of the disease, tumor size or stage; 5) It can monitor the tumor treatment effect and tumor recurrence; 6) It can predict the prognosis of the tumor. The future development of tumor markers is mainly to improve specificity and sensitivity [7].

3. Classification of tumor markers and their clinical application

Common tumor markers include: embryonic antigen tumor markers, carbohydrate antigen tumor markers, enzyme tumor markers, protein tumor markers, viral tumor markers. These tumor markers will be further explored next.

3.1 Embryonic antigen tumor marker

3.1.1 Alpha-fetoprotein (AFP）

Alpha-fetoprotein (AFP) is a glycoprotein that belongs to the albumin family and is mainly synthesized by fetal liver cells and yolk sac. Alpha-fetoprotein has a high concentration in fetal blood circulation, and it decreases after birth. From February to March, alpha-fetoprotein is basically replaced by albumin, which is difficult to detect in blood, so it is extremely low in adult serum. Serum alpha-fetoprotein content normal reference value: <25ug / L (25ng / mL). For newborns, if neonatal AFP is significantly elevated, it suggests neonatal hepatitis, congenital biliary atresia, or embryonic malignancies that secrete AFP. Decreased levels of AFP indicate the presence of chromosomal abnormalities (aneuploidy), such as trisomy, as well as Turner's syndrome, hydrocephalus, fetal growth restriction, etc[8-10].

Alpha-fetoprotein is closely related to the development of liver cancer and various tumors, and can exhibit high concentrations in various tumors (testicular cancer, ovarian tumor, malignant teratoma, pancreatic cancer, gastric cancer, intestinal cancer, lung cancer). Can be used as a positive indicator of a variety of tumors [11-15]. Generally, the increase in AFP content in benign liver disease is transient and generally lasts for 2-3 weeks. Malignant tumors continue to increase. Therefore, dynamic observation of serum AFP content can identify both benign and malignant liver diseases, as well as early diagnosis of liver cancer. At present, it is mainly used as a serum marker of primary liver cancer. 60% to 70% of patients with primary liver cancer in China are positive for AFP, which is used for the diagnosis and efficacy monitoring of primary liver cancer [16].

3.1.2 Carcinoembryonic antigen (CEA)

Carcinoembryonic antigen (CEA) is a tumor-associated antigen first extracted from colon and embryo tissues by Gold and Freedman in 1965. It is an acidic glycoprotein with human embryonic antigenic properties and is present in endoderm cells. The surface of differentiated cancer cells is the structural protein of the cell membrane [17]. It forms in the cytoplasm, is secreted outside the cell through the cell membrane, and then enters the surrounding body fluid. Therefore, it can be detected from various body fluids and excretions such as serum, cerebrospinal fluid, milk, gastric juice, chest and ascites, urine, and feces.

The normal reference value of carcinoembryonic antigen is <5.0ng/ml. In the past, CEA was used as a specific marker for early diagnosis of colon cancer and rectal cancer. After a lot of clinical practice, it was found that not only the CEA value of malignant tumors of gastrointestinal tract can be increased. It is also elevated in the serum of breast cancer, lung cancer and other malignant tumors [18]. Therefore, carcinoembryonic antigen is a broad-spectrum tumor marker, although it can not be used as a specific index for the diagnosis of a malignant tumor, but it still has important clinical value in the differential diagnosis, disease monitoring and therapeutic evaluation of malignant tumors [19].

3.2 Carbohydrate antigen tumor markers

3.2.1 Carbohydrate antigen 19-9 (CA19-9)

The carbohydrate antigen (CA19-9) is a mucin-type saccharide protein tumor marker, which is a glycolipid on the cell membrane and has a molecular weight of more than 1000 kD. In serum it exists in the form of salivary mucin, which is distributed in the normal fetal pancreas, gallbladder, liver, intestine, and normal adult pancreas, bile duct epithelium, and the like. It is a tumor-associated antigen of the gastrointestinal tract that exists in the blood circulation. Reference range: ≤37k U /L. The sensitivity in pancreatic cancer, gastric cancer, colon cancer, and liver cancer is 67% to 86% [20], 31.5% to 68% [21-22], 50% [23], 49% to 60.9% [24], respectively. The sensitivity in lung cancer and

breast cancer is low, about 10%. The positive rate is the highest in pancreatic cancer, and it is the most sensitive marker for pancreatic cancer reported so far.

3.2.2 Carbohydrate antigen 15-3 (CA15-3)

Carbohydrate antigen 15-3 (CA15-3) is a polymorphic epithelial mucin, a tumor cell-associated antigen secreted by secretory epithelial cells (eg, epithelial cells of the breast, lung, gastrointestinal tract, uterus). Normal human excreta can also be detected. In general, the reference value for CA15-3 is <28 U/ml. Up-regulation of tumor marker levels in tumor patients is often earlier than clinical manifestations [25], CA15-3 is often used as a specific marker for clinical breast cancer, and is a marker for breast cancer diagnosis, recurrence and efficacy evaluation [26]. It has been reported in the literature [27] that the detection of serum CA15-3 level has a relatively high sensitivity and specificity for the diagnosis of breast cancer metastasis, and the more metastatic lesions and the wider the range, the higher the CA153 level, the dynamic observation of its changes, Early detection of breast cancer recurrence or metastasis [28-29]. The study found that CA15-3 also increased in different degrees in other malignant tumors such as lung cancer, prostate cancer, ovarian cancer, cervical cancer and gastrointestinal cancer.

3.2.3 Carbohydrate antigen 12-5 (CA12-5)

The carbohydrate antigen CA125 (CA125) is a common hormone type in human body and the most studied ovarian cancer marker. It is often used for the diagnosis of ovarian cancer and the judgment of whether there is recurrence after surgery. The serum CA125 level of patients with ovarian cancer is significantly increased. The level of CA125 is rapidly decreased in patients with surgery and chemotherapy. If there is recurrence, the increase in CA125 may precede the clinical symptoms [30]. Other non-ovarian malignancies also have a certain positive rate, such as breast cancer 40%, pancreatic cancer 50%, gastric cancer 47%, lung cancer 44%, colorectal cancer 32%, and other gynecological tumors 43%.

3.2.4 Carbohydrate antigen 50 (CA50)

Carbohydrate antigen 50 (CA50) is a sialyl ester and sialoglycoprotein, which is not normally found in normal tissues. When cells are malignant, glycosylation enzymes are activated, causing changes in cell surface glycosylation and becoming CA50 markers. . Normal blood <20μg / L, many patients with malignant tumors can increase blood, such as 66.6% of lung cancer, 88.2% of liver cancer, 68.9% of gastric cancer, 88.5% of ovarian or cervical cancer, 94.4% of pancreatic or cholangiocarcinoma, More than 70% of other rectal cancers, bladder cancers are elevated [31].

3.3 Enzyme tumor marker

3.3.1 Neuron specific enolase (NSE)

Neuron specific enolase (NSE) is a protein with enolase activity in nerve tissue, which is specifically localized to neuron and neuroendocrine cells, and is a good indicator of neurological diseases and tumors. SCLC is a neuroendocrine-originated tumor. Therefore, NSE is one of the most valuable serum tumor markers of SCLC, with sensitivity ranging from 40% to 70% and specificity ranging from 65% to 80%. Study [32] found that patients with lung cancer with a serum NSE concentration of >10 μg / L were found in 70% of SCLC patients, but less than 20% in NSCLC patients. Normal human serum NSE levels <12.5μg / L. Currently, NSE has become one of the important markers of SCLC. It has been reported that [33] NSE is the most sensitive and specific tumor marker of NSCLC, and serum NSE determination can be used as a predictor of prognosis in patients with SCLC.

3.3.2 Prostate specific antigen (PSA)

Prostate specific antigen (PSA) is secreted by prostate epithelial cells and belongs to the family of kininase proteins. It is present in prostate tissue and semen, and its content in normal human serum is extremely small. In 1979, Wang et al. successfully extracted PSA from prostate tissue by immunoprecipitation [34], and conducted extensive and in-depth research on the value of PSA in early diagnosis, curative effect observation and prognosis of prostate cancer. [35-37]. At present,

PSA has become the most valuable and most valuable tumor marker for clinical research of prostate cancer.

3.4 Protein tumor marker

3.4.1 Cytokeratin 19 (Cyfra21-1)

Cytokeratin 19 (Cyfra 21-1) is a soluble fragment of cytokeratin-19. Cyfra21-1 is the preferred marker for non-small cell lung cancer, especially lung squamous cell carcinoma. Combined detection with CEA and NSE is of great value in the differential diagnosis and monitoring of lung cancer. Cyfra21- 1 is also a good indicator for the diagnosis and treatment of breast cancer, bladder cancer and ovarian cancer. Studies have shown that carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA21-1) have a sensitivity of 89% in evaluating the efficacy of advanced NSCLC [38].

3.4.2 Squamous cell carcinoma antigen (SCCA)

Squamous cell carcinoma antigen (SCCA) is a tumor-associated antigen extracted from cervical squamous cell carcinoma tissue, and the normal human serum content is extremely <2.5 μg/L. SCCA is a tumor marker for squamous cell carcinoma and is suitable for the auxiliary diagnosis, treatment observation and recurrence monitoring of cervical cancer, lung squamous cell carcinoma, esophageal cancer, head and neck cancer, and bladder cancer. Foreign literature reports that the detection of SCC-AG in serum has certain clinical significance for evaluating the extent of cervical squamous cell carcinoma, treatment effect and monitoring recurrence [39].

3.5 Viral tumor marker

Cytomegalovirus (CMV) enables cell transformation and is thought to be related to the development of human malignancies to some extent. Epstein-Barr virus (EBV) is the cause of infectious mononucleosis, and the occurrence of nasopharyngeal carcinoma and Burkitt's lymphoma is also closely related [40]. Hepatitis B virus (HBV) is closely related to the onset of liver cancer. It has indirect or direct carcinogenic effects. It has been reported that the incidence of liver cancer in HBsAg-positive patients is 216 times higher than that in HBsAg-negative patients. Hepatitis C and hepatitis D virus are also closely related to the occurrence of liver cancer. Herpes simplex virus HSV-2 is closely related to human cervical cancer. The positive rate of ESV isolation in women over 45 years old is 38%, while that in cervical cancer patients of the same age group is 61%.

4. Outlook and summary

Tumor marker detection has the advantages of simple method and no trauma, and has been paid attention to and recognized by the clinic. However, like other diagnostic methods, tumor markers are not the “universal key” for diagnosing tumors, but they are referenced for most patients. Or an important reference. The use of each tumor-associated antigen for the treatment of observation and prediction of recurrence is a useful indicator. Most indicators of dynamic observation can also be used for tumor recurrence prediction. Through the argumentation of this paper, it laid the foundation for the in-depth study of tumor marker diagnosis.

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