

Research article

Correlation between molecular markers and clinical pathology in colorectal cancer

Ping Zhu¹, ZhiJing Xing¹, CaiXia Ding², XiaoMin Wang², Lin Li^{1,2*}

1 Shaanxi University of Chinese Medicine, Shaanxi Xianyang 712046, China

2 Shaanxi Provincial Cancer Hospital, Shaanxi Xi 'an 710061, China

*Corresponding author

ABSTRACT

Immunohistochemical detection of colorectal cancer (CRC) plays a key role in guiding targeted therapy and assessing clinicopathological characteristics. This review focuses on the key immunohistochemical markers such as HER2, KRAS, NRAS, BRAF and PD-L1, and discusses the selection of targeted therapy drugs and the clinicopathological relationship. The overexpression of HER2 is associated with the invasion, metastasis and poor prognosis of CRC. Her2-targeted drugs such as trastuzumab provide a new way for the treatment. KRAS, NRAS, and BRAF mutations are similarly associated with a poor prognosis in CRC, but currently targeted agents targeting these mutations have had limited efficacy. As an immune checkpoint molecule, the high expression of PD-L1 is related to the immune response and prognosis of CRC.PD-L1 inhibitors have become an important tool for immunotherapy. Through the detection of these indicators, doctors can more accurately evaluate the tumor characteristics and prognosis of CRC patients, and formulate personalized treatment plans for patients. These

immunohistochemical markers not only provide a basis for targeted therapy of CRC, but also deepen our understanding of the clinicopathological characteristics of CRC.

Key words: colorectal cancer; PD-L1; c-Met; HER2; The RAS; BRAF

0 Background

Colorectal cancer (colorectal cancer, CRC) is a high incidence, poor prognosis of digestive system malignant tumor, according to 2022 cancer science progress released statistics: 2022 colorectal cancer number 517100, ranked second in the total cancer number, 240000 new deaths, ranked fourth in the cancer deaths of [1]. Colorectal cancer latency period is very long, with the development of the disease and deterioration, most of colorectal cancer patients progress to late will appear obvious symptoms, common symptoms including anemia, body quality, bowel habit change, abdominal pain, diarrhea, or constipation, etc., if not timely treatment, the risk of death back increased greatly. Therefore, early diagnosis and treatment can improve the patient detection rate and improve the prognosis. In addition, up to 50% of patients with localized colorectal cancer eventually transform into metastatic colorectal cancer (metastatic colorectal cancer, mCRC), and the most common metastatic organ is the liver, followed by lung and peritoneal [2]. At present, the commonly used detection methods for colorectal cancer include serum marker detection, computed tomography (computer tomography, CT) examination, magnetic resonance examination, anal diagnosis and fecal

occult blood test, but the final diagnosis of the disease is still based on pathological biopsy [3]. This article is mainly based on molecular markers and treatment.



Figure 1 China Cancer Data Statistics (a)



Figure 2 China Cancer Data Statistics (b)

1. Molecular markers

1.1 The mismatch repair proteins

Mismatch repair proteins (mismatch repair, MMR) include mismatch repair system homology 2 (muts homolog2, MSH 2), mismatch repair system homology 6 (muts homolog6, MSH 6), mismatch repair system protein 2 (postmeiotic segregation increased 2, PMS 2) and mismatch repair system homology 1 (mutl homolog 1, MLH 1). The expression of MLH 1, MSH 2, MSH 6 and PMS 2 were detected in tumor samples by immunohistochemistry. If all four MMR proteins were positive, they was complete mismatch repair function (mismatchrepairproficient, pMMR); any loss of MMR protein was defective mismatch repair function (mismatch repair deficiency, dMMR). Usually the dMMR is equivalent to the MSI-H phenotype, The pMMR is equivalent to the MSI-L / MSS phenotype, Microsatellite instability (microsatellite instability, MSI) is the formation of large numbers of frameshift mutations during DNA replication, causing changes in the number of nucleotide repeat units, If two or more of the five microsatellite loci are unstable. Is the microsatellite height instability (microsatellite-instability-high, MSI-H); If one microsatellite locus is unstable, Low-degree microsatellite instability (microsatellite-instability-low, MSI-L); If all of the five

microsatellite loci are stable, Then is the microsatellite stability (microsatellite stability, MSS), MSI [4] frequently occurs in CRC. A domestic study showed that dMMR in colorectal cancer patients occurred well in the right colon, mucinous adenocarcinoma tissue. Moreover, it was mainly related to tumor site and pathological type, but not related to age, sex, TNM stage, the presence of cancer thrombus in the vein and the presence of nerve invasion [5]. A domestic study based on colorectal cancer in young population found that dMMR expression had age difference, mainly in those <40 years, and the colorectal cancer type was mainly mucinous adenocarcinoma, and patients had a better prognosis [6]. Xiang Lin Guo et al [7] also found that the main factors affecting dMMR were patients with mucinous adenocarcinoma in the right colon <50 years old, and dMMR expression was associated with BRAF gene mutation and MSI-H.

1.2 Mutations in the KRAS, NRAS, and BRAF genes

The RAS gene is one of the most frequently mutated genes in human malignancies, mainly including three genes: KRAS, NRAS and HRAS. When the RAS gene activates the constitutive oncogene, its expression product Ras protein configuration is changed, and its ability to bind to guanosine diphosphate (GDP) is weakened, and guanosine triphosphate (GTP) can activate itself without the stimulation of external growth signals. The activated Ras protein continuously activates phospholipase C

(phos-pholipase C, PLC) to produce a second messenger, resulting in continuous cell proliferation and inhibition of cell apoptosis. The enhancement of cell-to-cell contact inhibition also accelerates this process, thus leading to the occurrence of cancer [8]. Wang Weicheng et al. [9] studied the clinicopathological characteristics of KRAS, NRAS and BRAF mutations in colorectal cancer, and found that the mutation rate of KRAS, NRAS and BRAF were 48.9%, 2.2% and 3.2%, respectively, and KRAS mutations were mainly associated with mucinous adenocarcinoma. Multivariate analysis indicated that BRAF mutations were associated with tumor location and mucinous adenocarcinoma. The NRAS mutations were associated with the T stage in the univariate analysis. Kras gene mutations are mainly found in colorectal cancer, with G12D mutation being the most common, and there are sex differences. Nras gene mutations account for a small proportion of colorectal cancer, but the Q61H mutation is the most common. Express dMMR in colon adenocarcinoma is usually accompanied by lymphocytic infiltration, and the most common type of deletion in dMMR is the combined deletion of MLH 1 and PMS 2. The most common gene mutation in colorectal cancer is the Kras gene mutation, and the most common mutation in BRAF mutation is BRAF V600E. Experiments have demonstrated that lymph node metastasis, KRAS mutation, BRAF mutation, and MSI-H are independent risk factors for poor prognosis in colorectal cancer patients

[10][11]. Du Jin et al. [12] found that Kras and BRAF gene mutations are related to TNM stage, and there is a negative correlation between Kras and BRAF gene mutations. KRAS, NRAS, NRAS, BRAF, PIK3CA and NTRK 1 can predict colorectal cancer recurrence. The combined test of these genes had the highest accuracy for the diagnosis of colorectal cancer recurrence, but the combination of KRAS, BRAF, PIK3CA and NTRK1 had the highest sensitivity, and the PIK3CA single test had the highest specificity.

1.3 c-Met protein

Interstitial epidermal transformation factor (c-Met) is an important receptor tyrosine kinase, and its excessive activation will cause the transformation of normal cells into tumor cells, and further promote the invasion of tumor cells. By immunohistochemical staining of c-Met protein in cancer tissues and adjacent tissues, [13] et al. found that the positive rate of c-Met in cancer tissues was higher than that of adjacent tissues, and the difference was statistically significant, and the positive rate of c-Met was correlated with disease course, clinical classification, and TNM stage. A foreign study found that [14] KRAS gene mutation could regulate the invasion response of colorectal cancer cells to fibroblast secreted factors through HGF / C-MET axis. When the KRAS gene expression was downregulated, the expression of c-Met and the cell response to HGF, thus reducing the aggressiveness of cancer cells.

Therefore, HGF / c-Met axis can be developed as a new therapeutic target. We found that miR-148a could inhibit angiogenesis and promote cancer cell apoptosis in colon cancer cells through direct downregulation of ROCK 1 and c-Met and their associated pathways. In addition, miR-148a also effectively inhibited the expression of vascular endothelial growth factor (VE GF) and myeloid leukemia 1 (Mcl-1). Meanwhile, miR-148a has a synergistic effect with bevacizumab (VE GF inhibitor) to promote apoptosis [15] in cancer cells. A domestic experiment using immunohistochemistry and bioinformatics analysis found that c-Met was not or poorly expressed in normal tissues, highly expressed in colon adenocarcinoma, and the expression level was negatively correlated with prognosis, with tumor angiogenesis, cell cycle,

Transfer showed a positive correlation. The c-Met chimeric antigen receptor T (CAR-T) cells can adsorb to tumor cells, and under antigen stimulation, CAR-T cells can kill cancer cells and release interleukin 2 (IL-2) and γ interferon (IFN- γ), which can directly kill tumor cells [16].

1.4 PD-L1

Programmed death ligand 1 (programmeddeathligand1, PD-L1) is a protein, mainly found on the surface of human cells, that regulates the immune system to regulate the autoimmune balance [17]. PD-L1 is

highly expressed in various malignant tumors, including lung cancer, breast cancer, colorectal cancer, gastric cancer, and bladder cancer [[18][19][20][21][22]. Detection of PD-L1 expression predicted tumor growth, spread, and metastasis. A domestic study found through immunohistochemistry experiment found that the expression level of PD-L1 in colorectal cancer was higher than that of normal tissues, and the expression level of PD-L1 was positively correlated with age, and the expression level of patients with lymph node metastasis was higher than that of those without metastasis. Through follow-up analysis, it was found that patients with positive PD-L1 expression had poor prognosis [23]. A foreign study made a comparison experiment between early onset colorectal cancer and late onset colorectal cancer, and the results show that the prognosis of early onset colorectal cancer is relatively late onset colorectal cancer is poor, and the incidence is increasing year by year. MSI-H incidence was higher in early-onset colorectal cancer, and was accompanied by early TNM stage, poor tissue differentiation, high PD-L1 expression, and higher incidence of mucinous adenocarcinoma [24].

1.5 HER-2

Human epidermal growth factor receptor 2 (human epidermal growth factor receptor 2, HER-2) is an important member of the epidermal growth factor (epidermal growth factor receptor, EGFR) family, which overexpresses [25] in various malignancies. In a domestic experiment

[26], the expression of HER-2 in colorectal cancer by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) technology found that HER-2 was expressed in colorectal cancer and colorectal adenoma, with no significant difference. The HER-2 positive expression was significantly higher in both colorectal cancer and colorectal adenoma than in adjacent tissues. However, the results of colorectal cancer, colorectal adenoma and adjacent tissues were compared by HER-2 (2 +). Positive HER-2 expression was not associated with sex, age, tumor diameter, and TNM stage. The HER-2 positivity rate was inversely proportional to the degree of tissue differentiation, and HER-2 expression was higher in colorectal cancer patients with lymph node metastasis.

2. Treatment

A foreign study found that a new therapeutic drug, perinone, suppressed KRAS gene mutation in colorectal cancer by increasing the percentage of apoptotic cells and G1 phase cells, and perinone can downregulate TP 53 and KRAS expression. Is expected to be a competitive therapeutic agent for [27] in colorectal cancer. It have found that patients with BRAF V600E mutation, c-MET amplification and TPM 4-ALK fusion. According to the knockdown of c-Met gene in SW 480 cells, some scholars found that the downregulation of c-Met gene expression could inhibit the expression of AKT 2, PIK3CA and MAP2K4 genes in the

HGF pathway, and then regulate the invasion and metastasis of colorectal cancer [29]. Some scholars have constructed a nomogram prediction model to study the prognostic factors of patients with targeted pMMR advanced colorectal cancer, and found that body mass index, cancer-inflammation prognosis index, systemic immune inflammation index, and carcinoembryonic antigen may be potential markers for the evaluation of immune combined targeted therapy for pMMR advanced colorectal cancer. Currently, surgery is the primary or preferred treatment for colorectal cancer that has not yet spread to distant sites. Chemotherapy e. 5-fluorouracil [5-FU] alone (i. other or fluoropyrimidines) or combination targeted therapy is the standard of treatment for patients with advanced CRC. FOLFOX (5-FU / oxaliplatin / leucovorin) and FOLFIRI (5-FU / irinotecan / leucovorin) are standard regimens for CRC chemotherapy, but colorectal cancer with dMMR expression has a poor prognosis after conventional chemotherapy and exhibits high levels of tumor neoantigens, tumor-infiltrating lymphocytes and checkpoint regulators. All of these features are correlated with the response of PD-1 blockade in other tumor types [31]. Therefore, we need to develop novel molecular markers or therapeutic targets.

PD-1 / PD-L1 immune checkpoint inhibitors are widely used in many types of cancer therapy. As a nuclear hormone receptor, peroxidase proliferator-activated receptor (PPAR δ) can regulate cell proliferation,

inflammation and tumor progression. A foreign study [32] found that PPAR δ antagonist GSK0660 significantly reduced the expression of PD-L1 protein and the transcriptional activity of PD-L1 gene in colon cancer cells. The reduced expression of PD-L1 in colon cancer cells can relieve the inhibition of T cell activity, and then enhance the body's immune response and lethality to tumor cells. Therefore, the combination of PD-1 antibodies and GSK0660 can effectively enhance colorectal cancer immunotherapy. It inhibited cancer cell migration and proliferation and induced apoptosis in tumor cells. A foreign study found that [33] heat shock protein 90 β (HSP90 β) is the direct target of toplasin. The low concentration of sand protein can reduce the activity of PD-L1 and improve T cell enrichment by regulating the HSP90 β -STAT 3-PD-L1 axis. Targeted therapeutic strategies can be used for human epidermal growth factor receptor 2 (HER 2) positive (amplified and / or excessive metastatic colorectal cancer). Currently, the first-line standard of care for patients with HER 2-positive metastatic colorectal cancer remains chemotherapy combined with epidermal growth factor receptor (EGFR) inhibitors or bevacizumab, depending on RAS / BRAF mutation status and side of the tumor. For patients with RAS / BRAF wild-type disease, HER 2-targeted drugs should be considered in subsequent treatment, and for patients who are not suitable for intensive therapy, HER 2-targeted drugs should be considered in first-line therapy,

cetuximab and panitumumab are two monoclonal antibodies against EGFR approved by the US Food and Drug Administration (food and drug administration, FDA) for combined first-line treatment [34] in patients with RAS wild-type metastatic colorectal cancer.

3. Discussion

Immunohistochemical detection of colorectal cancer plays a crucial role in the precision treatment of tumors. The detection of HER 2, KRAS, NRAS, BRAF, and PD-L1 not only provides a basis for the selection of targeted therapeutic drugs, but also has a close connection with the clinicopathological features. HER 2-positive colorectal cancer patients may be considered with targeted agents directed against HER 2, such as trastuzumab. These drugs block the growth and proliferation of tumor cells by inhibiting the HER 2 signaling pathway. HER 2 overexpression has been associated with the aggressive, metastatic, and poor prognosis of colorectal cancer. HER 2-positive colorectal cancers tend to have higher tumor stage and worse survival prognosis. KRAS, NRAS and BRAF are commonly mutated genes in colorectal cancer, and these mutations can affect the EGFR signaling pathway and thus affect tumor cell growth and spread. However, currently targeted drugs targeting these mutated genes have limited efficacy in colorectal cancer. Mutations in KRAS, NRAS, and BRAF have been associated with the aggressive, metastatic, and poor prognosis of colorectal cancer. These mutations are generally associated

with poorer tumor differentiation, higher rate of lymph node metastasis, and shorter survival. PD-L1 (programmed death ligand 1) is an immune checkpoint molecule that is associated with immune escape from tumor cells. Targeted drugs against PD-L1 (such as pabolizumab, navulumab, etc.) restore the anti-tumor activity of T cells by blocking the binding of PD-L1 and PD-1. The expression of PD-L1 is closely related to the immune microenvironment of colorectal cancer. Colorectal cancers with high PD-L1 expression tend to have more abundant tumor-infiltrating lymphocytes and a better immune response. Moreover, PD-L1 expression is also related with the stage, degree of differentiation and prognosis of colorectal cancer. In clinical practice, through the detection of these immunohistochemical indicators, doctors can more accurately evaluate the tumor characteristics and prognosis of colorectal cancer patients, and develop more personalized treatment options for patients. For example, for HER 2 and for colorectal cancer patients with high PD-L1 expression, for immunotherapy with PD-L1. Moreover, the detection of these indicators also helps to predict patient response and prognosis to specific treatment options, providing strong support for clinical decision making. It should be noted that immunohistochemical testing is only part of the precision treatment of colorectal cancer, and it also requires a comprehensive evaluation of the clinical findings, imaging tests and other laboratory tests. At the same time, with the deepening of medical research

and the progress of technology, more immunohistochemical indicators and targeted therapeutic drugs will be applied in the precision treatment of colorectal cancer in the future.

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