REVIEW

Progress in clinical diagnosis and treatment of colorectal cancer with rare genetic variants

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ABSTRACT   Targeted therapy is crucial for advanced colorectal cancer (CRC) positive for genetic drivers. With advances in deep sequencing technology and new targeted drugs, existing standard molecular pathological detection systems and therapeutic strategies can no longer meet the requirements for careful management of patients with advanced CRC. Thus, rare genetic variations require diagnosis and targeted therapy in clinical practice. Rare gene mutations, amplifications, and rearrangements are usually associated with poor prognosis and poor response to conventional therapy. This review summarizes the clinical diagnosis and treatment of rare genetic variations, in genes including erb-b2 receptor tyrosine kinase 2 (ERBB2), B-Raf proto-oncogene, serine/threonine kinase (BRAF), ALK receptor tyrosine kinase/ROS proto-oncogene 1, receptor tyrosine kinase (ALK/ROS1), neurotrophic receptor tyrosine kinases (NTRKs), ret proto-oncogene (RET), fibroblast growth factor receptor 2 (FGFR2), and epidermal growth factor receptor (EGFR), to enhance understanding and identify more accurate personalized treatments for patients with rare genetic variations.

KEYWORDS   Genetic variation; gene mutation; gene amplification; gene rearrangement; targeted therapy

Introduction

With rapid progress in advanced sequencing techniques, such as comprehensive genome sequencing in clinical applications, genetic testing has been generally recommended for the diagnosis and treatment of patients with colorectal cancer (CRC)[1]. Increasing numbers of biomarkers, such as KRAS, BRAF, and microsatellite instability (MSI) status, are being used to guide prognostication and treatment decision-making. Moreover, genetic changes in receptor tyrosine kinases are found in 2%–7% of colon cancer cases[2-4]. Many patients may have clinically undetected changes in oncogenic driver genes and therefore may benefit from targeted therapy.

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Rare genetic variations are those detected in fewer than 10% of patients. These rarely detected biomarkers are widely acknowledged to reflect genetic complexity and variations[5], including point mutations, amplification, and activation rearrangements. Targeting these biomarkers and developing personalized treatment regimens has considerable potential in metastatic CRC (mCRC) therapy.

Nonetheless, surgery, radiation before surgery, or neoadjuvant chemotherapy determined by cancer stage and tumor location, remain the main mCRC treatments[6]. However, increasing evidence indicates that the addition of targeted drugs to treatment regimens confers more benefits and prolongs survival. For example, the VEGFR-2 binding monoclonal antibody ramucirumab in combination with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) significantly increases overall survival (OS) and progression free survival (PFS) beyond that observed with placebo plus FOLFIRI[7]. The addition of cetuximab to 5-fluororuracil, leucovorin, and FOLFIRI has been shown to increase median PFS in patients with previously untreated wild-type RAS[8]. Moreover, combined application of immune checkpoint inhibitors and targeted drugs has shown promising clinical prospects, and may
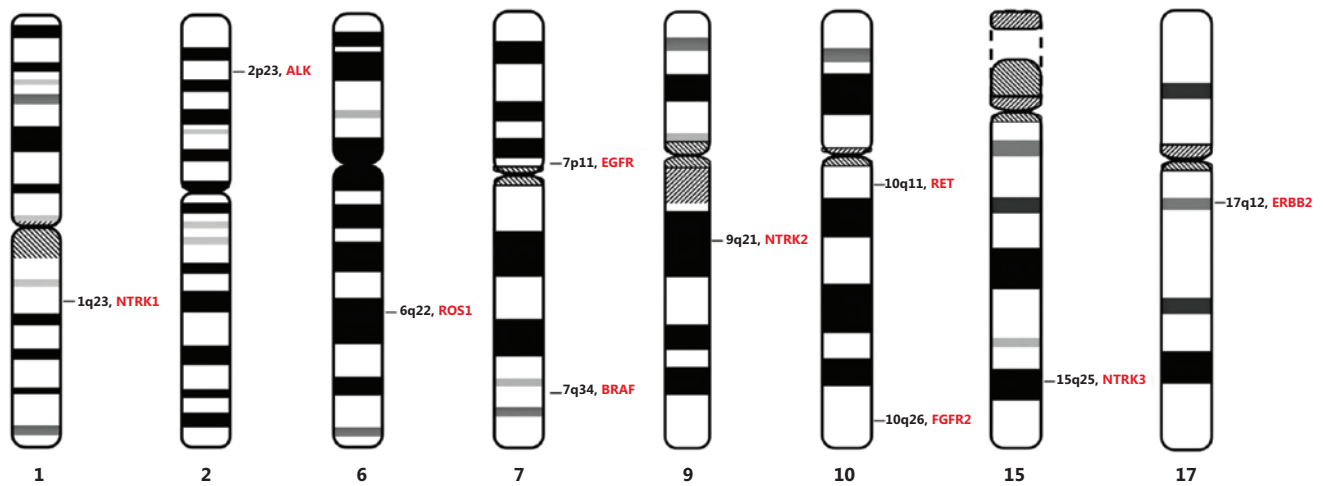
Figure 1 Chromosomal localizations of rare mutated genes in CRC described in this review.

Table 1 CRC rare genetic variations and prognosis

Gene	Chromosomal location	Major variation	Frequency	Mutation site/partner gene	Prognosis
ERBB2	17q12*	Mutation or amplification	5%–7%[11,12]	S310F, L755S, V777, V8421, L866M[12]	Benefit from anti-HER2 therapy
BRAF	7q34*	Mutation	10%[13]	V600E[14-16]	Benefit from targeted therapy
ALK/ROS1	2p23, 6q22*	Fusion or amplification	0.05%–2.5%[17-19]	*EML4, SPTBN1, CAD, SMEK2, TRN, SENPF, MAPRE3, PRKAR1A, C2orf44, PPP1R21*, etc.[17,20]	Benefit from inhibitor therapy
NTRKs	1q23, 9q21, 15q25*	Fusion	0.2%–2.4%[21]	*ETV6, TPM3, LMNA, TPR, IRF2BP2*, etc.[21]	Benefit from targeted therapy
RET	10q11*	Fusion	0.4%[22,23]	*CCDC6, NCO4, TNIPI, SNRNP70*, etc.[22,23]	Poor prognosis in patients with positive fusion
FGFR2	10q26*	Amplification	4%–5%[24]	S26P, D283N, W290C, S252W, K310R, A315T, S372C, Y375C, etc.[24]	Benefit from targeted therapy
EGFR	7p11*	Mutation	1%[25]	Ser492[25,26]	Benefit from targeted therapy

*https://www.ncbi.nlm.nih.gov/gene/.

lead to new treatment strategies and achieve extended survival times. For instance, combined application of PD-1 and BRAF inhibitors has been found to enhance response rates and survival[9,10].

This article reviews the clinical diagnosis and corresponding treatment strategies of rare genetic variations (**Figure 1**) (including gene mutations, amplifications, and rearrangements) in CRC, so that patients with rare genetic variations can receive more precise and individualized treatment (**Table 1**).

ERBB2 gene mutation or amplification

ERBB2, also known as HER2, encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. HER2 somatic mutation or amplification is present in 5%–7% of patients with CRC[11,12]. HER2 point mutation sites, including S310F, L755S, V777L, V842I, and L866M, are increasingly being reported[12]. These mutations
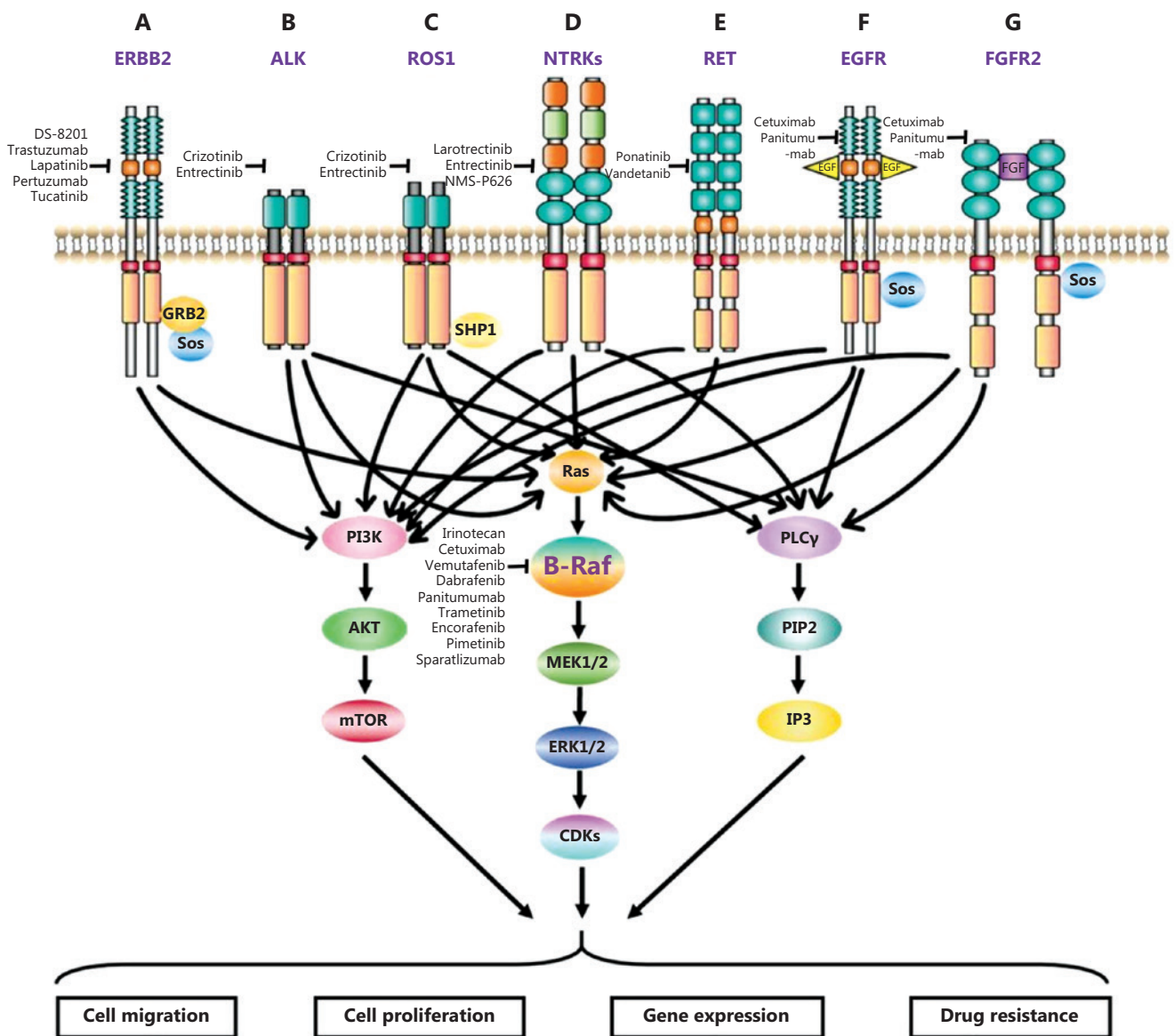
Figure 2 Expression products and effects of rare mutated genes in CRC. (A) ERBB2 (HER2), (B) ALK, (C) ROS1, (D) NTRK1, NTRK2, and NTRK3, (E) RET, (F) EGFR, and (G) FGFR2 activate Ras-Raf-MAPK, PI3K-AKT, and PIP2-IP3 signaling pathways and ultimately facilitate cell migration, cell proliferation, gene expression, and drug resistance.

and amplifications of HER2 have been found to activate downstream signaling pathways (**Figure 2A**) and generate primary resistance to EGFR monoclonal antibody therapy[11,27].

The DESTINY CRC01 study, first reported in 2021[28], used a novel antibody-drug conjugate, trastuzumab deruxtecan (DS-8201), to treat patients with mCRC with HER2 overexpression (HER2 3+ or HER2 2+ in IHC and FISH positive). The study included patients with mCRC with wild-type RAS and BRAF who had previously undergone 2 or more treatment regimens.

This efficient regimen achieved an objective response rate (ORR) of 45.3% (24/53), a median PFS of 6.9 months, and a median OS of 15.5 months. In 2023, the researchers further reported no responses in the IHC HER2 2+ and FISH negative group and the IHC HER2 1+ group[29].

HERACLES, a multicenter, open-label phase II study, has revealed the efficacy of trastuzumab combined with lapatinib for the dual targeted therapy of refractory wild-type KRAS and HER2 positive mCRC[30]. Among 913 patients, 44 were

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Table 2 Clinical experiments involving ERBB2 and BRAF variation targeted therapies

Gene	Research	Phase	Treatment	Inclusion criteria
ERBB2	DESTINY CRC01 (NCT03384940)	II	DS-8201	ERBB2 amplification with wild-type RAS/BRAF
	HERACLES (EudraCT 2012-002128-33)	II	Trastuzumab + lapatinib	ERBB2 amplification with wild-type KRAS
	HERACLES-B (NCT03225937)	II	Trastuzumab + lapatinib pertuzumab + T-DM1	ERBB2 amplification with wild-type KRAS/BRAF
	MyPathway (NCT02091141)	IIa	Pertuzumab + trastuzumab	ERBB2 variations
	MOUNTAINEER (NCT03043313)	II	Trastuzumab + tucatinib	ERBB2 amplification with wild-type RAS
BRAF	Irinotecan + cetuximab ± vemutafenib (NCT01787500)	Ib	Irinotecan + cetuximab ± vemutafenib	BRAF V600E mutation with wild-type KRAS
	SWOG S1406 (NCT02164916)	II	Irinotecan + cetuximab ± vemutafenib	BRAF V600E mutation
	Combined research on BRAF/MEK/EGFR inhibitor (NCT01750918)	I/II	Dabrafenib + panitumumab + trametinib	BRAF V600E mutation
	BEACON (NCT02928224)	III	Encorafenib + cetuximab ± pimetinib	BRAF V600E mutation
	Dabrafenib + trametinib + PDR001 (NCT03668431)	II	Sparatlizumab + dabrafenib + trametinib	BRAF V600E mutation

HER2+ (4.8%), and had an ORR of 35% and a median PFS of 5.5 months. Patients with higher HER2 gene copy numbers had better chances of survival after anti-HER2 treatment. No clear HER2 detection standard in CRC was available until HERACLES proposed using the IHC/FISH method to detect HER2 expression. HER2 positivity was defined as ≥ 50% cells with HER2 3+ or 2+ in IHC and FISH positivity (HER2: CEP17 ≥ 2); these criteria are more stringent than the diagnostic standards for breast cancer and gastric cancer.

A later version of HERACLES, the HERACLES-B study, added wild-type BRAF as a criterion[31], and used a more potent combination of pertuzumab and T-DM1 (an antibody-drug conjugate coupled with trastuzumab and emtansine) for treatment. The ORR of 9.7% was lower than the preset primary endpoint (ORR 30%). In addition, the stability rate of the condition was 67.7%, and the median PFS was 4.1 months. Although the results of this study were negative, this new anti-HER2 treatment showed promising therapeutic prospects, with PFS benefits similar to those in the previous HERACLES study (4.2 months) and excellent safety.

MyPathway, a multicenter phase IIa study in multiple cohorts, has evaluated the efficacy of targeted therapeutic drugs in patients with tumors with HER2, BRAF, EGFR, or Hedgehog pathway activation[32]. In a subset analysis, patients with refractory mCRC with HER2 genetic variations (amplification, mutation, or overexpression) were treated with pertuzumab and trastuzumab. The ORR of the 57 enrolled patients with mCRC reached 32%, a value similar to the ORR in the HERACLES study. The results received substantial attention.

MOUNTAINEER is a multicenter, single arm clinical trial similar to the previous studies. The enrolled patients had wild-type RAS mCRC accompanied by HER2 amplification or over-expression, and prior chemotherapy and anti-VEGF treatment were ineffective. After treatment with trastuzumab combined with tucatinib (a highly selective oral small molecule kinase inhibitor of HER2), the ORR was evaluated. As of April 2019, 22 of 26 enrolled patients had completed evaluations, the ORR was 55%, and the clinical benefit rate was 64%. The median PFS was 6.2 months, and the median OS was 17.3 months. This study harvested the most effective outcome in mCRC patients who were treated with anti-HER2 therapy, thus indicating the strong potential of this treatment regimen[33]. On the basis of the results, researchers have expanded the scope of the experiment to better evaluate ORR and safety. The final results, reported in 2023, indicated an ORR of 38.1%, and hypertension (7%) as the most common adverse event. No deaths were attributed to adverse events[34]. These findings support the continued exploration of targeted therapy in HER2-positive mCRC (**Table 2**).

BRAF gene mutation

Another genetic variation with crucial clinical significance is BRAF. The BRAF gene is located on chromosome 7q34 and encodes the RAF kinase, which is involved in the MAPK/ERK

signaling pathway (**Figure 2**)[35,36]. In V600E, the most common BRAF gene mutation, the amino acid at position 600 in the CR3 kinase domain of BRAF is changed from valine (V) to glutamate (E)[14-16]. This mutation causes activation of the MAPK pathway, thus initiating downstream gene transcription and leading to unlimited cell proliferation and metastasis[37]. Approximately 10% of patients with mCRC have BRAF gene mutations, of whom approximately 90% have the BRAF V600E mutation. These types of CRC mutations are poorly differentiated, and the tumors are mucinous, and prone to lymph node and peritoneal metastasis[38-40]. This phenomenon is more common in older women and is correlated with high microsatellite instability (MSI-H)[38].

Evidence supports that patients with BRAF gene mutations, compared with wild-type BRAF, have poorer prognosis and scarcely half the survival times after routine treatment[39,41]. However, the hazard ratio of BRAF mutation indicates dynamic effects over time. Specifically, BRAF mutation is a risk factor during the first 10 months of second-line treatment but subsequently becomes a protective factor; therefore, its influence is not time-invariant[42].

Although KRAS is often described simultaneously with BRAF and has a similar role in the MAPK pathway[13], its mutation frequency is approximately 35%–40%[43]. However, discussion of KRAS is beyond the scope of this review.

Since the approval of BRAF inhibitors such as vemutafenib and dabrafenib by the US Food and Drug Administration (FDA) for the treatment of unresectable or metastatic melanoma with BRAF mutations, BRAF inhibitors have been highly anticipated to be applied for the treatment of mCRC[14]. However, BRAF inhibitors have poorer efficacy in mCRC mono-therapy than observed in BRAF mutated melanoma, with an ORR of only approximately 5%. However, their combination with other targeted therapies such as antibodies to EGFR, MEK inhibitors, or PI3K inhibitors, has great potential[14,44]. In a phase Ib study, 35% (6/17) of patients with mCRC with BRAF mutations and wild-type KRAS showed remission in imaging examinations using different doses of veimofenib combined with irinotecan and cetuximab (VIC regimen), with a median PFS of 7.7 months[45].

On the basis of the success of the phase Ib study, Kopetz et al. began to explore whether the VIC regimen might be more effective than the IC regimen in patients with mCRC with BRAF mutations. The SWOG S1406 study[46] randomly divided 106 patients with mCRC with BRAF mutations who had previously received 1 or 2 regimens into 2 groups receiving systematic treatment with the VIC regimen or the IC regimen. Preliminary vemurafenib addition improved the PFS (median PFS: 4.4 months *vs.* 2.0 months). The ORR and disease control rate (DCR) were also significantly higher in the VIC group than the IC group (ORR: 16% *vs.* 4%, $P = 0.09$; DCR: 67% *vs.* 22%, $P < 0.001$). The VIC combined chemotherapy regimen is not affected by previous irinotecan treatment, MSI status, PIK3CA mutation, or tumor site. Moreover, the combination of vemurafenib remains effective in patients who show progression after VIC treatment. The final results of the 2020 SWOG S1406 study indicated that the addition of cetuximab combined with irinotecan significantly prolongs median PFS, ORR, and DCR[46], thus providing hope to patients with mCRC with BRAF mutations.

Another open-label phase I/II study has evaluated the efficacy of BRAF/MEK/EGFR inhibitors in 142 patients with mCRC with BRAF mutations, and shown encouraging results. The ORR was better with triple drug combination therapy than dual drug targeted combination therapy (21% *vs.* 0), but the median OS was not prolonged (9.1 months *vs.* 8.2 months)[47]. Similarly, BEACON, an open-label, global, three-arm phase III clinical study, has yielded similar results[48]. That study evaluated the safety and efficacy of combined encorafenib plus cetuximab, with or without pimetanib, in the treatment of patients with BRAF V600E mutated mCRC who progressed after 1–2 previous regimens. The 665 enrolled patients were randomly divided into a triple drug targeted group, a dual drug targeted group, or a control group receiving cetuximab combined with irinotecan or FOLFIRI (1:1:1). Compared with that in the control group, the median OS was significantly prolonged (9.3 months *vs.* 5.9 months), and the ORR was significantly improved (26.8% *vs.* 1.8%), in the groups receiving combination therapy with 3 or 2 drugs. Furthermore, the incidence of adverse events was also reduced (57.4% *vs.* 65.8%) compared to the control group[48]. On the basis of the results of the BEACON study, the FDA first approved dual target therapy, and the 2021 NCCN guidelines also recommended encorafenib in combination with cetuximab or panizumab for second or posterior line treatment of patients with BRAF mutated CRC.

Combined treatment with BRAF and immune checkpoint inhibitors has shown promising efficiency. A phase II clinical trial has combined PD-1, BRAF and MEK inhibition with sparatlizumab (PDR001), dabrafenib, and trametinib in 37 patients with BRAF V600E CRC[9]. The combination of PD-1, BRAF, and MEK inhibition yielded more than threefold greater

cORR (25%) than historical controls with combined BRAF/MEK inhibition alone (7%). Combination immune checkpoint targeted therapy may provide new ideas for future CRC treatment. The above results provide a foundation for the future exploration of targeted therapy for BRAF V600E (**Table 2**).

Fusion genes produced by kinase rearrangement

Beyond gene amplification, gene fusion also has a major role in genetic variation. The production of fusion genes through genomic rearrangement of protein kinases has been reported in CRC, although the type and probability of occurrence remain unclear[49]. A study in the United States has conducted comprehensive genome sequencing analysis in 18,407 CRC samples and 513 ctDNA samples. Kinase rearrangements (KREs) were identified in 126 CRC tissue samples (0.68%) and 7 ctDNA samples (1.36%). The most common kinases included RET (22%), BRAF (22%), NTRK1 (16%), and ALK (13%). Other rare KREs included EGFR, FGFR1-3, ROS1, RAF1, NTRK2-3, PDGFRB, and MET[17,49,50]. A total of 52% (69/133) of patients with KRE are women, with a median age of 62 years. In KRE cases, the most common non-kinase gene mutations are TP53 (67.7%), APC (39.1%), RNF43 (30.1%), and MLL2 (21.1%), whereas 90% of cases have wild-type KRAS status[49].

ALK/ROS1 gene rearrangement

ALK gene rearrangement is rare in patients with CRC, occurring a frequency of 0.05%–2.5%[18-20]. The companion genes reported in ALK fusion include EML4, SPTBN1, CAD, SMEK2, STRN, SENPF, MAPRE3, PRKAR1A, C2orf44, and PPP1R21[18,51]. Compared with wild-type ALK, which requires ligand binding to activate kinase activity, ALK fusion proteins activate downstream signal transduction pathways (such as the STAT3, AKT, and MAPK pathways) without ligand binding, thereby promoting cancer cell proliferation and metastasis (**Figure 2B**)[17].

Patients with ALK rearranged CRC primarily have wild-type KRAS, BRAF, EGFR, and ERBB2 genes. Common mutations are rarely observed[52,53]. ALK targeted therapy is expected to provide clinical benefits for this patient population. The limited number of patients with such rearrangements has hindered clinical trials.

Nonetheless, case reports have described patients with CRC with ALK fusion responding to ALK targeted therapy[20,51]. For example, patients with STRN-ALK gene rearranged mCRC have been reported to benefit from the ALK/ROS1 inhibitor crizotinib[54,55], whereas patients with CAD-ALK gene rearrangement have been found to benefit from the ALK/ROS1/NTRK inhibitor entrectinib[56,57]. Beyond gene rearrangement, reports have indicated amplified ALK gene copy numbers in 3.4% of patients with CRC. Increased ALK gene copy number is closely associated with poor prognosis in patients who do not respond to EGFR monoclonal antibody treatment[58,59]. Although patients with glioblastoma with ALK amplification have been reported to benefit from ALK inhibitor treatment[60], whether patients with CRC might benefit from ALK inhibitor treatment requires further in-depth research. ALK rearrangement can be detected not only through IHC, FISH, and NGS, but also in the ctDNA of patients with CRC, thus providing a new approach for non-invasive detection of gene rearrangement in patients[61,62].

Receptor tyrosine kinase (ROS1) belongs to the sevenless subfamily of tyrosine kinase insulin receptor genes. Owing to the high similarity in the active sites between ALK and ROS1[63,64], ROS1 also activates the MAPK/ERK, PI3K/AKT, and PIP2/IP3 signaling pathways (**Figure 2C**). ROS1 fusion, including SLC34A2-ROS1 fusion and GOPC-ROS1 fusion, occurs in 0.2%–2.4% of CRC cases[61]. Additionally, ROS1 is considered a driver in microsatellite stable CRC[65,66]. ALK inhibitors are expected to be used for the treatment of patients with ROS1 gene rearranged mCRC[57,61,67].

NTRK gene rearrangement

The NTRK gene family of neurotrophic tyrosine kinase receptors consists of 3 members: NTRK1, NTRK2, and NTRK3, located on chromosomes 1q23, 9q21, and 15q25, respectively. The corresponding encoded proteins are TrkA, TrkB, and TrkC[68]. NTRK gene fusion is caused by chromosomal variation, thereby resulting in the fusion of members of the NTRK gene family with other unrelated genes[69-71]. The TRK fusion protein is constitutively activated, thus triggering a cascade reaction of downstream signaling pathways and driving tumor development (**Figure 2D**).

Older women, and individuals with MSI-H, and right colon and lymph node metastasis, are at high risk of NTRK gene fusion, whereas most have wild-type status of BRAF and other genes. Moreover, MSI-H status is found in 30%–35% or

more of patients with ALK, ROS1, and NTRK gene rearrangements,[21,71]. In the future, research is expected to elucidate the molecular mechanisms underlying the correlation between MSI status and kinase gene rearrangement.

The rate of NTRK gene rearrangement in CRC ranges from 0.2% to 2.4%, and involves primarily TPM3-NTRK1, EML4-NTRK1, and LMNA-NTRK1[72]. The rearrangement of TPM3-NTRK1 was first discovered in colon cancer 30 years ago but has not received widespread attention. A recent study has detected the TPM3-NTRK1 rearrangement junction region and revealed a 1.5% incidence rate of TPM3-NTRK1 gene rearrangement in patients with CRC.

At the 2017 American Society of Clinical Oncology (ASCO) and the 2018 European Society of Oncology (ESMO) annual meetings, the NTRK targeted drug larotrectinib (LOXO-101) was reported to have effective outcomes in patients with NTRK gene fusion[73]. The new Trk inhibitor entrectinib has also shown an outstanding ORR of 57.7% (95% CI 36.9–76.7), according to the final results reported in 2022[74,75]. The TrkA small molecule inhibitor NMS-P626 underwent preclinical research indicating promising clinical application prospects[76]. Patients with CRC with ALK, ROS, and NTRK gene rearrangements have poor prognosis and initial non-response to EGFR monoclonal antibody treatment, thus partially explaining the limited benefits of EGFR monoclonal antibodies in patients with right colon wild-type RAS/BRAF tumors. Therefore, for patients with right-sided colon lesions with ALK, ROS, or NTRK gene rearrangements, in addition to considering corresponding targeted treatment, intensive regimens such as FOLFOXIRI combined with bevacizumab may also be a reasonable first-line treatment choice[61].

Fusion gene testing is not currently routinely used in mCRC treatment, thus potentially leading to missed diagnosis in patients with gene rearrangements. The standardized process for detecting gene rearrangement in the future must be further confirmed. Applying simple and feasible methods such as immunohistochemistry for initial screening, and then conducting complex tests, such as qPCR, FISH, and sequencing, to confirm gene rearrangement in patients may be a cost-effective detection strategy. In contrast, given the high proportion of patients with ALK/ROS/NTRK gene rearrangement in the MSI-H state, more treatment options may be available for targeted therapy and immunotherapy combination treatment in the future[61,69].

Other rare genetic variations

In this section, 3 types of receptor tyrosine kinase variations are briefly introduced. The RET gene encodes a tyrosine kinase receptor (**Figure 2E**)[22]. RET gene fusion tends to be observed in older people, and those with right colon wild-type RAS/BRAF and MSI-H tumors, accounting for 0.4% of mCRC cases[23,77]. Patients with mCRC with RET gene fusion have poor prognosis, with an average OS of approximately 14 months. The multi-target inhibitors ponatinib and vandetanib have achieved effective results in a patient driven tumor xenograft model with RET gene fusion[78].

The FGFR gene, belonging to the same tyrosine kinase receptor family as EGFR (**Figure 2F**), encodes the fibroblast growth factor receptor, and contributes to tumor proliferation and progression (**Figure 2G**)[79]. FGFR2 amplification occurs in approximately 5% of gastric cancer cases and 4%–5% of CRC cases. NGS technology has been used to detect FGFR amplification in patients with CRC; consequently, the FGFR/STAT pathway serves as a therapeutic target. EGFR mutation is infrequent in CRC and often occurs in patients with secondary resistance to cetuximab[24,26]. After treatment with cetuximab, some patients experience mutations in the extracellular segment of EGFR (Ser492), thus preventing effective binding of cetuximab to the extracellular segment of EGFR[25]. Consequently, downstream signaling pathway activation cannot be inhibited by cetuximab, thus leading to tumor progression. The EGFR Ser492 mutation does not affect binding between panitumumab and EGFR, and, inhibitory effects on the downstream pathway persist. Therefore, for patients with such mutations, switching to panitumumab can achieve therapeutic effects[25]. After treatment, the EGFR p.S492R mutation has been detected in 1% of patients treated with panitumumab *vs.* 16% of those treated with cetuximab[80]. Gene amplification of CDK, encoding a molecule downstream of EGFR and FGFR, is among the most common changes in cancer, and has an incidence rate of 5%–40% in various tumors[81,82]. CDK amplification has also been reported in patients with CRC, with an approximately 20% incidence rate[83]. CDK inhibitors (CKIs) inhibit tumor growth by targeting cell cycle proteins. Dozens of CKIs have been reported, such as DUX4, CKS1, and CKS2[84]. The successful application of CKIs is expected to profoundly affect the treatment of many solid tumors, including CRC.

However, not every rare genetic variation in CRC is a known risk factor or is correlated with poor prognosis. For example,

in LEP and LEPR, some mutated haplotypes present at relatively low frequencies have been associated with prolonged OS and DFS among patients with CRC[85].

Conclusions

Rare genetic variations, unlimited cell proliferation, and chromosomal instability play major roles in CRC progression. Rare genetic variations, such as mutations in ERBB2, BRAF, and EGFR, can drive CRC initiation and progression by disrupting normal cellular processes and promoting uncontrolled growth[86]. In contrast, unlimited cell proliferation and chromosomal instability are hallmarks of cancer cells including CRC[87]. These processes can lead to the accumulation of genetic alterations, genomic instability, and the development of more aggressive cancer phenotypes. In summary, whereas these factors all contribute to CRC progression, rare genetic variations initiate hallmark features including unlimited cell proliferation and chromosomal instability. Thus summarizing the rare genetic variations in CRC is important.

Many clinical and experimental trials are focusing on the discovery of biomarkers and the development of targeted drugs. Although biomarkers are increasingly being recognized, their incidence remains low. Targeted treatment regimens have been applied in patients with CRC with HER2 amplification as well as BRAF V600E mutations in clinical practice. Furthermore, several principles must be followed in targeted therapy. KRAS, NRAS, and BRAF mutations have poor response to EGFR targeted treatment. Even in patients with wild-type KRAS, NRAS, and BRAF, approximately 40% do not respond to EGFR monoclonal antibody treatment, thus indicating that other oncogenic driving factors may play key roles in these patients.

Overall, the future development of technology is expected to provide more precise molecular diagnosis for patients, with the potential to identify more therapeutic targets and develop corresponding drugs. Thus, patients with rare genetic variants of CRC are likely to receive more personalized treatment.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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