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Review

Towards a precision immune checkpoint blockade immunotherapy in patients with colorectal cancer: Strategies and perspectives

Guanglin Cui [a,b,*]

[a] Research Group of Gastrointestinal Diseases, the Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[b] Faculty of Health Science, Nord University, Campus Levanger, Norway

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ABSTRACT

To date, immune checkpoint blockade (ICB) immunotherapy has become one of promise strategies in the management of patients with unresectable or metastatic colorectal cancer (CRC). However, clinical observations showed that not all the patients responded equally to ICBs, certain group of CRC patients with microsatellite-instability-low (MSI-L) phenotype was not sensitive to ICB immunotherapy. In addition, some primary responders might lose their sensitivity and become resistant to ICBs overtime. To obtain a better response rate and therapeutic efficacy, considerable attempts have been made toward to a precision medicine algorithm. Studies showed that multiple strategies based on the patient's individual condition might improve the response and therapeutic efficacy to ICBs. Therefore, we focused on and discussed precision strategies and perspectives e.g., how to early define candidates who will benefit from ICB immunotherapy prior treatment, overcome the primary and acquired resistance and improve the therapeutic response to ICBs in CRC patients with different microsatellite-instability statuses within the context of precision medicine algorithm in this review.

1. Introduction

Colorectal cancer (CRC) is the third prevalent human cancer and the second leading cause of cancer-related death in developed countries [1]. Recurrence and metastasis are the main death reasons in patients with CRC. Therefore, how to treat unresectable or metastatic CRC patients is a critical clinical issue for the prolong of patients' life. More recently, immune checkpoint blockades (ICB) e.g., monoclonal antibodies for programmed cell death receptor 1 (PD-1) and its ligand (PD-L1), cytotoxic T-lymphocyte associated protein 4 (CTLA4) were developed and become one of promise therapeutic strategies in the treatment of unresectable or metastatic CRC patients, and showed a significantly improved the therapeutic efficacy [2–6]. However, clinical data also showed that not all the CRC patients are equally sensitively to ICBs [7,8]. For example, distinct response rates to ICBs were found between CRC patients with mismatch repair-proficient (pMMR)/microsatellite-instability-low (MSI-L) and CRC patients with mismatch repair-deficient (dMMR)/microsatellite-instability-high (MSI-H) sub-phenotypes [9–11]. Studies of mechanisms suggested that multiple factors e.g. tumor mutational burden (TMB), PD-1/PD-L levels and

Abbreviations: CAMK1D, the calcium/calmodulin-dependent protein kinase 1D; CD8 T cell-H, higher population of CD8 T cells; CRC, colorectal cancer; ctDNA, circulating tumor DNA; CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T-lymphocyte associated protein 4; dMMR, mismatch repair-deficient; DNMTi, DNA methyltransferase inhibitors; FMT, fecal microbiota transplantation; ICB, immune checkpoint blockades; IDO, indolamine 2′3′-dioxygenase; IFN-γ, interferon-γ; IFN-γ-H, higher population of IFN-γ; ICB, immune checkpoint blockade; IHC, immunohistochemistry; IL, interleukin; Immunosuppressive cell-H, higher population of immunosuppressive cells; IRC, immune-related response criteria; IRF2, interferon regulatory factor 2; LAG3, lymphocyte-Activation Gene 3; mAb, monoclonal antibody; MDSCs, myeloid-derived suppressor cells; MSI-H, microsatellite-instability-high; MSI-L, microsatellite-instability-low; MSS, microsatellite-stable; NGS, next-generation sequencing; ORR, the objective response rate; OS, overall survival; PD-1, programmed death-1 receptor; PD-L1, programmed death-1 receptor ligand; PD1/PD-L1-H, higher level of PD1/PD-L1; PD1/PD-L1-L, lower level of PD1/PD-L1; PFS, progression-free survival; pMMR, mismatch repair-proficient; smMIPs, single-molecule molecular inversion probes; TILs, tumor infiltrating lymphocytes; TGF-β, transforming growth factor-beta; TGGA, the cancer genome atlas; TIL, tumor infiltrating lymphocyte; TMB, tumor mutational burden; TMB-H, higher amount of tumor mutational burden; TMB-L, lower amount of tumor mutational burden; Treg, regulatory T cell.

* Correspondence to: Faculty of Health Science, Nord University, Campus Levanger, Norway or Research Group of Gastrointestinal Diseases, the Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China.
E-mail address: guanglin.cui@nord.no.

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microenvironmental immunological features might contribute to such distinct response rates in CRCs with different microsatellite-instability statuses [8,12–14]. In addition, clinical studies revealed that some primary responders might lose their sensitivity overtime and finally become acquired resistance to ICBs [15–18]. All these evidence in turn draws a attention to a necessary for optimized ICB immunotherapy within the context of precision medicine.

Indeed, considerable attempts to the early identify a sensitive CRC patient who will benefit from ICB immunotherapy prior treatment, and strategies that can overcome the primary and acquired resistance and convert a non-responder to a responder to ICBs have been made [19,20]. Therefore, we summarize the current strategies and efforts that improve the ICB immunotherapy within the context of precision medicine in this review. In addition, we discuss perspectives with great clinical interest that will lead to a novel breakthrough in ICB immunotherapy and result in a better management in patients with CRC.

2. Search strategy and selection criteria

2.1. Literature search strategy and overview

Relevant electronic literature search was conducted in academic databases PubMed, MEDLINE and Google scholar by the author using the search terms “colorectal cancer”, “metastasis”, “dMMR”, “pMMR” and “MSI”, “immune checkpoint inhibitor”, “anti-PD-1”, “anti-PD-L1”, “anti-CTLA4”, “response”, “biomarker”, “personalized” and “precision” from inception to October 2021. Articles selected from reference lists of appropriate papers as an additional literature source were included.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) articles published in English; (2) full-text available; (3) studies or trials of ICBs performed in both animal and human CRCs.

Exclusion criteria: (1) articles published as abstract or non-full text publications (case reports, editorials, letters to editors, or meeting abstracts); (2) studies were rejected if they lacked sufficient information to study ICBs in CRC.

3. The early identification of candidates who will benefit from ICB immunotherapy in patients with CRC

Clinical analysis showed that the majority of CRC patients were primary or acquired resistance to ICBs [12,13,21]. To avoid unnecessary offer of ICBs to a non-responsible patient, predictive biomarkers can provide supportive information to early define a responsible CRC patient prior to the ICB immunotherapy. Currently, several biomarkers are used for the identification of ICB-sensitive CRC patients.

3.1. MSI sub-phenotypes

Based on MSI genetic mutation patterns, CRCs can be characterized as two sub-phenotypes: dMMR/MSI-H and pMMR/MSI-L [22–24]. As previously reported that the majority of CRCs were pMMR/MSI-L sub-phenotype that unresponsive to ICBs, only 15% of CRCs were dMMR/MSI-H sub-phenotype and response to ICBs at a rate of approximately 30–40% [22,25,26]. Such distinct sensitivity to ICBs leaded to clinicians prefer to select an CRC patient with dMMR/MSI-H sub--phenotype as a candidate for ICB immunotherapy prior to treatment by MSI genetic testing [6,27,28].

Despite extensive data describing the importance of MSI phenotype as a main biomarker for the selection of candidates for ICB immunotherapy [29,30], its limitations have also been discussed. For example, the primary response rate to ICBs in dMMR/MSI-H CRCs was only 30–40% [21,31–34], over 50% of dMMR/MSI-H CRCs still failed to response effectively to the ICB immunotherapy [35]. In addition, some primary responder might lose of the sensitivity to ICBs overtime [21, 31–34]. Researchers have hypothesized that other biomarkers such as tumor mutation burden (TMB) and populations of immune cell infiltration might add help to identify the unresponders in patients with CRC [17, 36–39].

3.2. TMB

TMB has emerged as a predictive biomarker of responsiveness to ICBs in patients with CRC [40–42]. Clinical results generated from metastatic CRC patients indicated that TMB level in CRCs with dMMR/MSI-H phenotype was significantly higher than CRCs with pMMR/MSI-L phenotype [41, 43–45], and likely associated with a better response to ICBs [40, 41, 46–50]. Recently, Li et al. [51] reported that tumor mutation score defined as the number of genes with mutations in candidate genes was better than TMB to predict the response to ICIs in patients with non-small cell lung cancer. Therefore, TMB could be used as an additional biomarker for the identification of sensitive candidates for ICB immunotherapy in patients with dMMR/MSI-H CRC.

3.3. Populations of immunosuppressive cells and CD8+ T lymphocytes within the CRC tumor microenvironment (TME)

Based on the findings of distinct immune scores and cellular phenotypes in the TME between dMMR/MSI-H CRCs and pMMR/MSI-L CRCs (23, 52, 53), the population of immune cells, such as immunosuppressive cells and CD8 + T lymphocytes, reside in the TME has been postulated as a biomarker candidate to predict the response to ICBs [52].

The population of immunosuppressive cells might display a predictive potential in the CRC with ICB immunotherapy. Several studies reported that a higher proportion of immunosuppressive cells predicted a poor response to ICBs [53], which was associated with the suppression of IFN-γ secretion and cytotoxicity of CD8-positive T cell function in CRC [54]. Toor et al. [55] demonstrated that a high population of Tregs was associated with a low response rate to ICBs in patients with CRC. Studies also revealed that populations of immunosuppressive cells i.e., Tregs and myeloid-derived suppressor cells (MDSCs) in the TME of dMMR/MSI-H CRCs were higher than pMMR/MSI-L CRCs [56–59]. Interestingly, an increased population of tumor-infiltrating Tregs and a reduced population of effector T cells in the CRC TME were associated with a high PD-1 expression level, which were reversed by ICBs [60,61].

Previous studies showed that CD8 + T lymphocytes played an regulatory effect on PD-1/PD-L1 expression and host immunity [62]. Recently, researchers found that the population of infiltrating CD8 + T lymphocytes might provide supportive information to predict the response to ICBs in patients with cancer [63–65]. Studies showed that FOLFOX chemotherapy enhanced the response to ICB immunotherapy through an effect on CD8 + T lymphocyte accumulation within the TME in a mouse model of CRC expressing a human tumor antigen [63]. Functional analysis revealed that CD8 + T lymphocyte exhaustion (a dysfunctional state for T lymphocytes in response to persistent antigenic stimulation) presented one of the major hurdles to ICB immunotherapy [66], and leaded to a fail response to ICBs [67]. Tian et al. [68] confirmed that CD8 + T lymphocyte exhaustion might predict the hyporesponsive state to ICBs, and be used as an differentiate biomarker between anti-PD1 resistance and anti-PD1 sensitive patients in CRC. Hu et al. [69] successfully characterized a population of pre-exhausted CD8 + T cells in CRC tumor tissues during exhaustion, which provided new insights into the mechanism of T-cell exhaustion and suggested that exhausted T cells within the TME accounted for the failure of immunotherapy in CRC [69]. Currently, many novel subsets of immune cells have been identified and were highly aggregated in the CRC TME [70]. However, similar to other predictive biomarkers e.g., cytokines and PD-1/PD-L1 levels, how to identify a cut-value of immune cell populations in the TME that can precisely identify the response to ICBs in patients with cancer remains a critical issue.

3.4. Immune checkpoint molecular levels

Studies reported that the measurement of PD-1/PD-L1 levels in patients with cancer provided essential predictive information to assess the sensitivity to ICBs prior to treatment [71–73]. Indeed, quantitative data showed that elevated levels of PD-1/PD-L1 predicated a high response rate to ICBs in CRC patients with dMMR/MSI-H [34, 72, 74–82]. Chen et al. [83] recently reported that CRC patients with higher expression of PD-L1 tended to have a more effective response to ICBs. To provide a better predictive index for the selection of ICB candidates in patients with CRC, further explorations are needed to define cut-values of PD-1 or PD-L1 levels or positive cell populations in the tumor mass. Further, many new immune checkpoint molecules are identified. The predictive value of these novel molecules as biomarkers remains to be investigated.

3.5. Cytokine expression levels

As essential mediators, cytokines play an critical role in the regulation of host anti-tumor immune response [70], and PD-1/PD-L1 expression [84]. It, therefore, holds potential as a predictive biomarker for the evaluation of response to ICBs. Studies in CRC mice with progressive liver metastasis showed that blockade of transforming growth factor-beta (TGF-β) signaling significantly enhanced the response to anti-PD-1/PD-L1 immunotherapy [85]. Several studies reported that an elevated expression level of interferon (IFN)-γ, an cytokine produced by activated T lymphocytes, prior to treatment in patients with melanoma or renal cell carcinoma predicted the positive response to anti-PD-L1 mAb [86–88]. IL-8 also held potential as a biomarker for the selection of patients who will benefit from ICB immunotherapy [89], and predicted the sensitivity to anti-PD-1 therapy in certain types of cancer [90,91]. IL-17A produced from both TH17 cells and other types of immune cells is an inflammatory cytokine involved in the initiation and progression of CRC [70]. We previously identified that the expression of IL-17A and its upstream stimulators was significantly increased in patients with CRC [92,93]. Notably, studies demonstrated that the activation of IL-17A signal could upregulate the expression of PD-1 in CRC cells [84], and predicted the un-responsiveness to anti-PD-1 immunotherapy in patients with microsatellite-stable (MSS) CRC [38]. More recently, Xi et al. [94] reported that IL-22 upregulated PD-L1 expression in human colon cancer cells and IL-22 expression level correlated well to PD-L1 expression at mRNA level in human colon cancer tissues, which was via the signal transducer and activator of transcription 3 signaling pathway [94]. Therefore, it would be interestingly to see whether IL-17A or IL-22 expression levels could help identify candidates and predict the response for ICB immunotherapy in patients with CRC in the future.

Despite some cytokines hold potential as predictive biomarkers for the selection of sensitive candidates and evaluation of response to ICBs, however, due to the complex of cytokine network in patients with CRC [95], the validation of cytokines as predictive biomarkers remains to be conducted in large population of CRC patients.

3.6. Novel biomarkers

In some studies, the predictive value of above biomarkers for the response to ICB immunotherapy in patients with CRCs has been challenged. For example, Le Flahec et al. [96] found no significant difference in PD-L1 expression levels between dMMR and pMMR CRCs in either whole tumor specimens or tissue microarray CRC slides. Such inconsistent results might be explained by the complex formation of TME and a mixture cellular source of PD-L1. Because of many factors i.e., the orientation of CRC sections might affect the counting of PD-1/PD-L1 positive cell population, how to standard the counting method and section quality remain to be studied. In addition, multiple immune checkpoint molecules are involved in the regulation of host immunity. For example, lymphocyte-activation gene 3 (LAG3) is another immune checkpoint molecule highly expressed in immune cells and significantly inhibits host antitumor immunity by negatively regulating T lymphocyte activation and cytokine secretion [37]. Studies have shown that the overexpression of LAG3 predicted the prognosis in patients with CRC [97]. Therefore, the measurement of LAG3 expression level prior to ICB treatment might help the clinicians understand immunosuppression phenotypes and statuses in patients with CRC.

Recently, the usefulness of other novel biomarkers for the prediction of response to ICBs have sequentially been tested in the CRC. For example, current research works have now emphasized a potential relationship between the altered gut microbiome profile and the sensitivity to ICBs. Several studies revealed that changes in composition of gut microbiome potentially influenced the efficacy of ICB immunotherapy by modulating the host immune response in cancer patients [98–100], and the supplementation of certain probiotics might improve the therapeutic efficacy and reduce the risk of death [101]. Therefore, primary resistance to ICBs in patients with tumor could be attributed to an abnormal gut microbiome. Examination of composition and function of gut microbiome in patients with cancer prior to treatment might predict the response to ICBs and manipulation of gut microbiome profile, of gut microbiome, for example by fecal microbiota transplantation (FMT) from normal objects, could increase the response rate to immunotherapies in patients with CRC [102]. However, despite available evidence of an association between the gut microbiome and the response to immunotherapies, the exact species of gut microbiome that can determine the response to ICBs in the treatment of recurrent and metastatic CRCs remain largely unexplored.

Liao et al. [103] recently reported that expression level of KRAS-interferon regulatory factor 2 (IRF2) axis predicted the response to ICBs. They found that CRC with higher IRF2 expression had an increased response rate to ICB (anti-PD-1) immunotherapy [103]. In addition, studies showed that circulating tumor DNA (ctDNA) might serve as a sensitive biomarker for assessing of TMB and predicating response to systemic therapies including ICB immunotherapy in patients with cancer [104]. Therefore, it would be particularly interesting to validate the predictive value of these novel biomarkers in large population of CRC patients with ICB immunotherapies in the future.

Overall, several biomarkers appear promising in the identification of sensitive candidates for ICB immunotherapy but are indeed not ideal. In the step of candidate identification before immunotherapy, a wise strategy is to combine MSI test with other biomarkers, thereby maximizing its effect in predicting sensitive response to ICBs in patients with CRC [29]. Incorporating integrated analysis of current published data, we summarized the role of current predictive biomarkers used in the identification of sensitive CRCs for ICB immunotherapy in Fig. 1.

4. Potential strategies for the management of lost response or acquired resistance to ICBs in a primary responder CRC with dMMR/MSI-H

Although dMMR/MSI-H CRCs are currently considered as main candidates for ICB immunotherapy [22,25], however, primary response rate to ICBs in CRC patients with dMMR/MSI-H is only 30–40%, and some of initial responders will lose their sensitivity and become resistant to ICBs overtime [21, 31–34]. Therefore, acquired resistance is an inevitable obstacle that significantly deceases the therapeutic efficacy and frequently increases the relapse rate of CRC patients after ICB immunotherapies [15–18]. To overcome resistance and enhance the response to ICBs in CRC patients with dMMR/MSI-H, different strategies have been developed.

4.1. Double or many combinational ICBs

Monotherapy of anti-PD-1 mAB may not block all the immune checkpoint pathways/signals, the combination of two or several ICBs

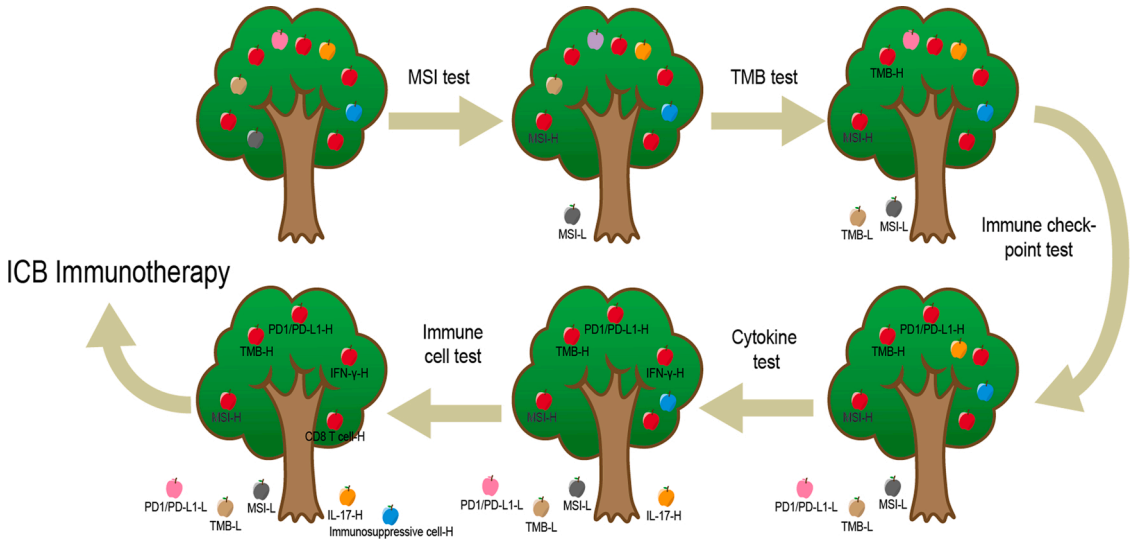

Fig. 1. Schematic summarized the postulated flow of predictive biomarker tests used in the identification of sensitive candidate for ICB immunotherapy in patients with CRC, incorporating integrated analysis of current published data. Combing with clinical features, a set of predictive biomarkers could help the clinicians to excluded CRC patients with unsensitive biomarkers e.g., microsatellite-instability-low (MSI-L), lower amount of tumor mutational burden (TMB-L), lower level of PD1/PD-L1 (PD1/PD-L1-L), higher level of IL-17-hight (IL-17-H) and higher population of immune suppressive cells (immune suppressive cell-H) from ICB immunotherapy. Finally, only CRC patients with sensitive biomarkers e.g., microsatellite-instability-high (MSI-H), higher amount of tumor mutational burden (TMB-H), higher level of PD1/PD-L1 (PD1/PD-L1-H), higher level of IFN-γ (IFN-γ-H) and higher population of CD8 T cells (CD8 T cell-H) were included for ICB immunotherapy.

increases the response rate to ICBs in patients with CRC (refer to summary in a recent review [31]). For instance, nivolumab combined with ipilimumab (anti-CTLA-4) antibodies enhanced clinical outcome in dMMR/MSI-H mCRC patients [47]. Therefore, double or many combinational ICBs were considered as potential treatment options for dMMR/MSI-H metastatic CRCs resistance to ICB monotherapy [31].

4.2. *Combinations of ICBs with other anti-tumor bioagents/therapeutics*

Accumulative evidence pointed to the future direction of ICB immunotherapy by a combination strategy with other antitumor therapies. Several trials for ICBs with other anti-tumor therapies or bioagents are currently ongoing, preliminary results showed that such combinations improved the immunological conditions in the TME and thereby enhanced the therapeutic efficacy in CRC patients with ICB immunotherapies [45,47,63,105,106]. For example, a phase 2 trial evaluated the therapeutic efficacy of combining pembrolizumab (antiPD-1) with chemotherapy (mFOLFOX6) in patients with untreated or unresectable CRC [107]. Results revealed that combing treatment induced partial responses in 15 CRC patients. Notably, a CRC patient with dMMR showed an complete pathological response after 2 months of therapy [107]. Cai et al. [108] reported that the combination of an anti-PD-1 monoclonal antibody with a angiogenesis inhibitor monoclonal antibody (apatinib) resulted in an enhanced therapeutic response in Balb/c mice bearing CT-26 colon cancer cells. Furthermore, a study reported that anti-PD-1 monoclonal antibody plus cancer-favoring oncolytic vaccinia virus exhibited an enhanced therapeutic effect in an mouse CRC model [109]. Combining ICBs with an antibody-IL2 fusion protein also showed an enhanced anti-tumor effect in immunocompetent mice bearing CT26 colon cancer cells [110]. The improved therapeutic efficacy of ICBs combined with other anti-tumor bioagents in CRCs with dMMR/MSI-H has been summarized in two recent reviews [31,111].

4.3. *Manipulating the profile of gut microbiome*

Several studies contributed to the understanding of the effect of resident commensal microbiome on the regulation of host immune function, and results showed that changed composition of microbiome effectively affected the therapeutic responses to ICB immunotherapy in cancers [98, 99, 102, 112–116]. Therefore, manipulating the profile of gut microbiota has been hypothesized as a promising strategy to improve the effectiveness of ICBs in patients with cancer [98,112]. Davar et al. [117] recently evaluated whether manipulating the profile of gut microbiota through fecal microbiota transplantation (FMT) could alter the resistance to anti-PD-1 in 16 PD-1-refractory melanoma patients. Indeed, their data showed that FMT together with anti-PD-1 monoclonal antibody could significantly change the gut microbiome profile and reprogrammed the TME to overcome resistance to ICB, and resulted in a positive response in 6 of 15 patients [117]. Recently, Ferrere et al. [118] reported that ketogenic diet and its principal ketone bodies induced compositional changes of the gut microbiota and improved the therapeutic response to immunotherapy with an anti-PD-1 antibody in a preclinical mouse aggressive melanoma model. Above findings suggest that a personalized modulation of gut microbiome pattern by diet or FMT may be a promising approach to improve the therapeutic response in CRC patients with ICBs.

For the convenience for readers, we summarized current strategies that improved therapeutic effect of ICBs in acquired resistant CRCs with dMMR/MSI-H in Fig. 2.

5. Potential strategies for the management of primary resistance to ICBs in CRCs with pMMR/MSI-L

Multiple studies demonstrated that CRC patients with pMMR/MSI-L that constituted ~85% of CRC cases did not benefit from ICB immunotherapy alone [2, 4, 28, 47, 119–129]. Therefore, how to turn a un-responsible pMMR/MSI-L CRC to a responsible CRC is vital in the era of precision ICB therapy [6,130]. Currently, multiple strategies have been postulated:

5.1. *Anti-LAG3 ICB immunotherapy*

LAG3 is a new immune checkpoint molecular that involved in the suppression of host anticancer immunity [97]. Zhou et al. reported that pMMR CRCs with liver metastasis had a high level of LAG3 in TILs and

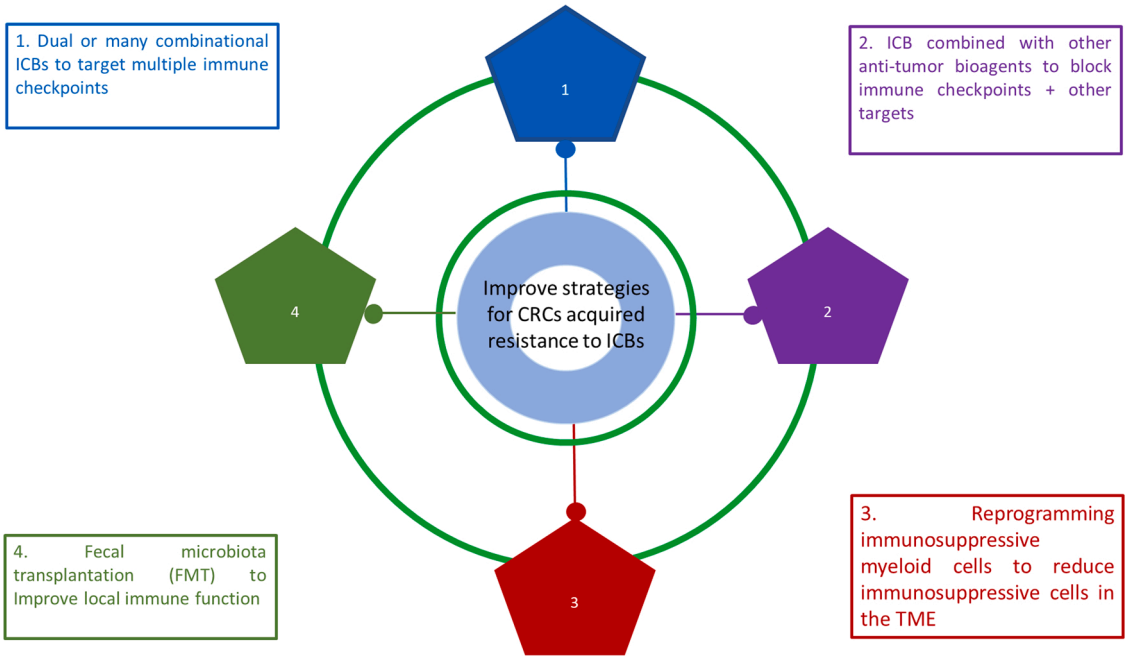

Fig. 2. Potential strategies and relevant mechanisms postulated to improve the response to ICBs in a acquired resistant CRC with dMMR/MSI-H.

targeting LAG3 signaling using an anti-LAG3 monoclonal antibody significantly enhanced activation and functional response of TILs [131]. Preliminary results from a phase 1 clinical trial of anti-LAG3 antibody favezelimab plus anti-PD1 antibody pembrolizumab showed that favezelimab alone or in combination with pembrolizumab were safety and well tolerance in advanced CRC patients with microsatellite stability phenotype [132]. It would be interesting to see final results from this clinical trial.

5.2. Combined ICBs with other anti-cancer bioagents

Potential synergistic roles of ICBs with other anti-cancer bioagents, such as antiangiogenic antibodies, have been demonstrated [34,133]. Wang et al. [133] recently demonstrated the synergistic efficacy of fruquintinib (a novel anti-EGFR tyrosine kinase inhibitor) plus anti–PD-1 monoclonal antibody for MSS CRC in a murine syngeneic model bearing CT26 colon cancer cells, in which a deeper suppressed tumor growth and a longer survival time were observed in tumor bearing mice treated with fruquintinib plus anti–PD-1 monoclonal antibody as compared to mice treated with the single drug alone.

5.3. Combined with radiation

Since cancers with a highly TMB and neoantigens are more sensitive to response to ICBs [134], how to increase the TMB has been discussed. Recently, Lussier et al. [135] reported that radiation was able to increase the expression of mutant proteins and neoantigens, which synergically increased the sensitivity to ICB immunotherapy in treated Kras (G12D) x p53(-/-) sarcoma cell lines in vitro. Twyman-Saint Victor et al. [136] further confirmed increased sensitivity to ICBs e.g. CTLA4 and PD-1/PD-L1 antibodies in combination with radiation based on pre-clinical models. A phase II trial of pembrolizumab plus radiotherapy or ablation conducted in pMMR metastatic CRC patients showed that pembrolizumab treatment one week after the completion of palliative radiation to a metastatic site showed an improved response [137]. In restectable liver metastatic CRC patients, Turk et al. [138] reported that pembrolizumab in combination with radiotherapy was safety and did not increase the relevant toxicity. These findings suggest that ICBs combined with radiation can improve the therapeutic efficacy in cancer patients with a low amount of TMB as seen in pMMR/MSI-L CRCs.

5.4. Modifying epigenetic dysregulations

Inhibition of epigenetic pathways, such as histone modification and DNA methylation, may augment TMB, neoantigens and restores immune recognition and immunogenicity. For example, Tu et al. [139] reported that low-dose decitabine (a specific DNA methyltransferase inhibitor) enhanced the therapeutic efficacy of anti-PD-1 mAb, in which a significant enhanced inhibitory effect on tumor growth and prolongation of survival time were observed in mice bearing CT26 colon cancer cells as compared to tumor bearing mice treated either with decitabine or PD-1 mAb alone. Further data revealed that such improved efficacy was associated with upregulated expressions of immune-related genes and cytokine genes as well as increased population of lymphocytes within the TME [139]. Recently, a human clinical trial reported that DNA methyltransferase inhibitors azacitidine and the histone deacetylation inhibitor entinostat in combination with pembrolizumab induced an improved therapeutic response to ICB in patients with MSS metastatic CRCs [31]. More recently, Wang et al. showed that that inhibition of N (6)-methyladenosine (m(6) A) mRNA modification by depletion of methyltransferases, Mettl3 and Mettl14, could significantly improve the response to anti-PD-1 therapy in pMMR/MSI-L CRCs [140].

5.5. ICBs combined with cytokine antibody

Previous studies suggested that the activation of IL-17A signal contributed to resistance to ICB immunotherapy in cancers, and ICBs combined with anti-IL-17 antibody might overcome resistance to ICBs [141]. Liu et al. [142] reported that IL-17A antibody combined with PD-1 antibody induced an enhanced response in both colitis-associated cancer and APCmin/+ MSS CRC murine models. ST2, a functional receptor for IL-33, has also been postulated to be a checkpoint target for CRC [143]. Studies showed that high ST2 expression was correlated with low CD8 + T cell cytotoxicity and poor survival in patients with CRC, combination of ST2 depletion with anti–PD1 monoclonal antibody resulted in an better inhibition efficacy in ST2-KO mice implanted with CRC [143]. Interestingly, we recently demonstrated that increased expression of ST2 was associated with the accumulation of Tregs in the

TME [144] that acted as an immunosuppressive factor to significantly affect the response to ICBs [61].

5.6. Re-modeling the CRC TME

Re-modeling the factors within the TME might help turn a "unsensitive" immunogenicity into a "sensitive" immunogenicity to ICBs in pMMR/MSI-L CRCs. Studies revealed that the tyrosine kinase inhibitor regorafenib significantly decreased the population of tumor-associated macrophages as compared to controls in the CT26 syngeneic mice [145]. Clinical trials showed an increased response rate in metastatic MSS CRCs in response to regorafenib [146] or in combination with durvalumab [NCT03539822; [31,129]]. The combinational target effects of the toll-like receptor 7/8 agonist NKTR-262, [NCT03435640; [31,129]], the CXCL12 antagonist olaptesed with nivolumab or pembrolizumab [NCT03168139; [31,129]] have also been tested, initial results demonstrated an enhanced response to ICBs in patients with metastatic MSS CRC [147].

Multiple actively recruiting clinical trials are currently being explored (see summary in recent reviews [31,129]), further results will help find more potential approaches that can turn a non-responsible pMMR/MSI-L CRC into a responsible CRC (refer to Fig. 3).

6. Conclusions and perspectives

Taken together with the existing research and clinical data in this review, a strong body of evidence suggested that multiple factors were involved in the mechanisms of CRC primary or acquired resistance to ICB immunotherapy, which led to a precision medicine consideration that ICB immunotherapy should be offered to right candidates. In the selection of candidates for ICB treatment, biomarkers were essential as it could provide appropriate guide for early identifying responsible patients and appropriate ICB immunotherapy. However, the power of a single biomarker in the identification of ICB candidates may be low. For example, many dMMR/MSI-H CRCs primarily identified as responders might loss the sensitivity to ICBs overtime. To maximize the power of current biomarkers in the selection of candidates, combining MSI test with other biomarkers into a practice "biomarker group" is necessary. Therefore, the power of MSI test with other biomarkers in larger population of CRCs with ICB immunotherapy needs to be further tested and validated in clinical practice.

Aiming to reduce the resistance and improve the clinical response in patients with different MSI sub-phenotypes, clinical studies have shown that dual ICB immunotherapies or ICBs combined with other anti-cancer strategies e.g., chemotherapy, radiotherapy, anti-angiogenesis bioagents have been initially evaluated and shown an improved response. Currently, several new immunologic suppressive cells/factors were the prominent force that could drive resistance to ICB immunotherapy in CRC have been identified [103,148]. Researchers recently revealed receptor EP4 for prostaglandin E2 as the main regulator of IMCs in suppressing response to ICB immunotherapy. Therefore, antagonist for EP4 might reprogram IMC function and enhance the response to ICB immunotherapy in CRC [53]. In addition, two studies reported that the m6A demethylase Alkbh5 may regulate the tumor cells refractory to ICB (anti-PD-L1) immunotherapy [140,149], however, the effects on regulating response to ICBs in patients with CRC remains to be investigated. In addition, new approaches that combined ICIs with co-stimulatory immune checkpoint molecules, such as CD28, OX 40 (CD134), and the tumor necrosis factor receptors family e.g., TNFRSF7 and TNFRSF9 has also been perspective. For example, OX40 is a strongly stimulator for the activation and proliferation of T lymphocytes [150]. Combinations of agents targeting OX40 with ICBs might enhance the activation and function of T lymphocytes and improve the therapeutic efficacy of ICBs in patients with CRC [150].

As new perspectives, preliminary results suggested that the manipulation of the gut microbiome by diet or FMT improved the immune and therapeutic response to ICBs and held a significant clinical potential. Till date, dynamics of the compositional and functional changes of gut microbiome in CRC patients with ICB immunotherapy are not fully known. Furthermore, the influence of different ICBs on gut microbiome profile changes and main species of gut microbiome that are selectively associated with resistance to ICBs in CRC have not been identified. Answers to these questions may help the researcher design novel precise FMT to improve the efficacy of ICBs based on the individual patient situation. Because the manipulation of the gut microbiome can be reached by diet intake [151], it is interesting to evaluate the effect of modifying the gut microbiota profile by diet on the therapeutic efficacy of ICB immunotherapy in patients with CRC in the future.

Emerging evidence suggests that many immune checkpoints participate in the suppression of antitumor immunity. Indeed, several novel

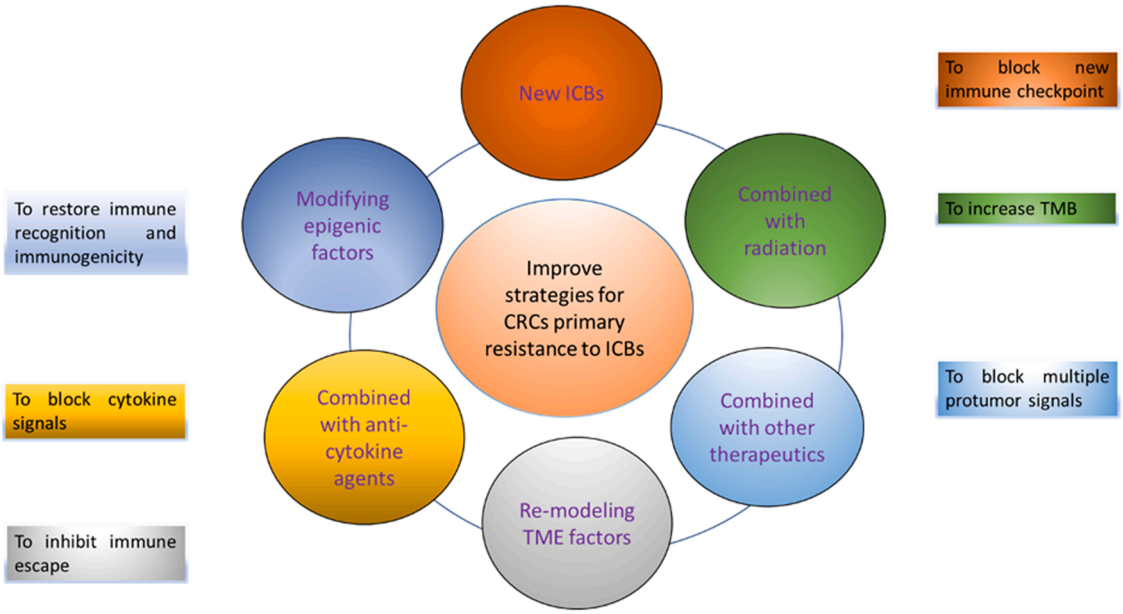

Fig. 3. Potential strategies and relevant mechanisms postulated for turning a nonresponse CRC to a responsible CRC to ICBs in primary resistant CRC with pMMR/MSI-L.

immune checkpoints, such as TIM-3, TIGIT, or VISTA, have been identified [152], studies revealed that these immune checkpoints was highly expressed on TILs and participated in the regulation of host anticancer immunity in patients with CRC [153]. In addition, the co-expression of PD-1 with these novel immune checkpoints was reported, and associated with a inhibited immunity via reduced expression of IFN-γ in tumor-infiltrating CD8 + lymphocytes in CRC patients [55,154]. These findings suggested that using monotherapy with a single anti-PD-1 monoclonal antibody might be not always enough to restore T-cells' functionality in patients with CRC [155]. Furthermore, V-domain Ig Suppressor of T cell Activation (VISTA) is an immune checkpoint with inhibitory effects on the function of T cells [156]. Studies showed that targeting VISTA using an anti-VISTA antibody restored the function and T cells and remolded the tumor stroma, which enhanced host anticancer immunity [157]. Preliminary results from studies of the anti-LAG-3 antibody in patients with advanced solid tumors showed that either the anti-LAG-3 antibody monotherapy or combination therapy with anti-PD1 antibody were well tolerated [158,159]. Many challenges remain. For example, to improve therapeutic efficacy, should all immune checkpoint pathways be blocked in patients with CRC ? Moreover, whether the clinicians can selectively offer a ICB to a CRC patient based on individual expression pattern of immune checkpoints is currently unknown, and how to optimize the current ICBs with novel ICBs also remains to be evaluated.

Finally, how to convert a non-responder to a responder to ICBs in CRC patients with MSI-L or MSS remains a big challenge. Modifying epigenetic dysregulations, such as DNA methyltransferase inhibitors azacitidine and the histone deacetylation inhibitor entinostat, enhanced the therapeutic efficacy of anti-PD-1 mAb in metastatic CRC patients with MSS [31]. These encouraged results might in turn help the researcher to design more powerful and specific epigenetic therapies in the future. Several studies also highlighted an improved response in some patients with pMMR/MSI-L CRC receiving combinational therapies compared to monotherapies. Therefore, more specific, and sensitive studies/trials with new combinational designs are required.

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CRediT authorship contribution statement

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Conflict of interest statement

The author declares that he has no competing interests related to this work.

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