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Targeting the tumour immune microenvironment for cancer therapy in human gastrointestinal malignancies

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ABSTRACT

Gastrointestinal (GI) cancer is a malignancy of the GI tract and accessory digestive organs. GI cancer patients develop resistance to chemotherapy, targeted therapy drugs and immune therapies. Although immune checkpoint inhibitors have shown promising clinical results in melanoma, etc., immune checkpoint blockade responds in only a subset of colorectal cancer (CRC) patients with microsatellite instability-high (MSI-H) tumours. The tumour immune microenvironment (TIME) has a dynamic nature during malignant progression to which all the cells in the TIME contribute. Recent studies have highlighted the role of the TIME in the therapy resistance of cancer. Immune suppressive cells, such as tumour-associated macrophages, regulatory T cells, and myeloid-derived suppressor cells, consist of a suppressive TIME to resist immune reactions. Combination approaches used to target the TIME, such as radiotherapy, chemotherapy, targeted therapy combined with checkpoint blockers or immune cell therapy, in addition to mono-immunotherapy, may provide better therapy responses. This review provides an analysis of recent developments regarding the role of the TIME in malignant progression, immunotherapy and the development of drug resistance in GI tract cancer, especially CRC, as well as approaches to overcome microenvironment-mediated resistance.

1. Introduction

Gastrointestinal (GI) cancers, including oesophageal, stomach, liver, pancreatic, small intestine, colon, rectal and anal, are among the most frequently occurring cancers worldwide. As one of the most commonly diagnosed cancers, colorectal cancer (CRC) is among the top 3 leading causes of cancer-related deaths, with an estimated 140,000 new cases and 50,000 deaths in the United States in 2018 [1]. Tumour malignant progression and metastases contribute to the high mortality of advanced CRC [2]. Furthermore, CRC patients develop resistance to chemotherapy [3], targeted therapy drugs [4] and immune therapies [5], which lead to increasing challenges in CRC treatment. Different kinds of immune cells in various cancer types were recently indicated to have an impact on tumour progression [6–10]. Some polarized immune infiltrates—with the ability to overturn adaptive immune responses—can stimulate proliferation in cancer cells and promote tumour angiogenesis, progression and metastasis [8]. For CRC, the responses to chemotherapy [11], radiotherapy [12], targeted therapies [13–15] and immunotherapy [16,17] are influenced by the immune system. CRC progression is also influenced by the intricate interaction between cancerous cells and the tumour microenvironment (TME) [18].

Additionally, both gastric and oesophageal cancers represent major global cancer burdens, ranking 2nd and 6th for the most common cause of cancer-related deaths [19]. Despite recent improvements in molecularly directed therapies, prognosis hovers around a median survival of 1 year in gastric cancer. Breakthroughs in immune checkpoint blockade offer potential therapeutic avenues, particularly with tools to overcome the mechanisms of immunosuppression in the TME [20]. Hepatocellular carcinoma (HCC), the most common primary hepatic malignancy, also faces increased incidence worldwide, with average

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Abbreviations

CRC	Colorectal cancer
NSCLC	Non-small-cell lung cancer
TME	Tumour microenvironment
TIME	Tumour immune microenvironment
MSI-H	Microsatellite instability-high
TAM	Tumour-associate macrophage
Treg	Regulatory T cell
DC	Dendritic cell
NK	Natural killer cell
CAF	Cancer-associated fibroblast
TEC	Tumour-associated endothelial cell
Th1	T helper type 1
Th17	T helper type 17
TGF-β	Transforming growth factor-β
M-CSF	Macrophage colony-stimulating factor
APC	Antigen-presenting cell
MDSC	Myeloid-derived suppressor cell
M-MDSC	Monocytic MDSC
G-MDSC	Granulocytic MDSC
EM-DR	Environment-mediated drug resistance
CAM-DR	Cell adhesion-mediated drug resistance
SFM-DR	Soluble factor-mediated drug resistance
TIL	Tumour-infiltrating lymphocyte
pMMR	Proficient mismatch repair
CMS	Consensus molecular subtype
SDF1A	Stromal cell-derived factor 1A
LAG-3	Lymphocyte activation gene 3
FGL1	Fibrinogen-like protein 1
HCC	Hepatocellular carcinoma
GI	Gastrointestinal

survival rates between 6 and 20 months [21]. HCC is particularly interesting to examine in the context of TIME targeting, given that more than 90% of patient cases arise in the context of injury and inflammation, yet immunotherapy has seen limited success [22]. Similarly, pancreatic cancer, the third leading cause of US cancer-related deaths, is not widely responsive to checkpoint therapy and merits examination of the complex TME for the more efficient use of immunotherapeutics [23].

The TME comprises various cell types (immune cells, fibroblasts, endothelial cells, etc.) and extracellular components (growth factors, cytokines, extracellular matrix, hormones, etc.) that surround cancerous cells [24]. Recent studies have highlighted that immune components in the TME can modulate tumour progression and are attractive therapeutic targets. These components are called the tumour immune microenvironment (TIME), which means that the TIME is one part of the TME [25–27]. The TIME has a dynamic nature during malignant progression, and all of the cells in the TIME contribute to this process. Immune suppressive cells, such as tumour-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs), suppress the TIME to resist immune reactions [28–30]. Multiple approaches of targeting the TIME, in addition to cancer cells, may be necessary for better therapy responses.

In this review, based on studies of human GI cancers, especially CRC, we provide an analysis of recent developments on the role of the TIME in malignant progression and metastasis, immunotherapy, and the development of drug resistance factors, mainly in CRC. In addition, potential approaches to overcome microenvironment-mediated resistance for CRC are also evaluated.

2. The role of TIME in tumour progression and metastasis in GI cancer

Many recent publications reported critical roles of TIME in GI cancers, including CRC, HCC, etc [18,22,31]. As an important determinant of tumour progression and outcome in GI cancers, the TIME is composed of various infiltrating immune cells, including TAMs, Tregs, MDSCs, dendritic cells (DCs), B lymphocytes and natural killer (NK) cells, as well as cancer-associated fibroblasts (CAFs), tumour-associated endothelial cells (TECs), the extracellular matrix and complicated vasculatures [28–30,32]. The TIME can shape cancer cell behaviours and therapy responses through interplay with cancerous cells via chemokine and cytokine signalling or direct contact [33–35]. Recent studies have highlighted that tumour progression and metastasis are regulated not only by genetic changes within tumour cells but also by the TIME elements [36–38]. For CRC, the most commonly diagnosed GI cancer, an increasing number of studies have attributed a poor outcome to MDSCs [39] B cells [40], T helper type 17 (Th17) cells [41,42] and M2 macrophages [43], while the presence of M1 macrophages [44], NK cells [45], T helper type 1 (Th1) cells [46,47] and DCs [48] have been shown to be associated with a good prognosis.

In Fig. 1, the TIME is depicted, and the dynamic nature of the immune contexture of a tumour is shown. Upon the recognition of tumour antigens, NK cells and DCs could be activated. NK cells could have an antitumour effect, while DCs could induce Tregs and increase IL-10, IL-35 and TGF-β secretion and then activate Th17 cells, which inhibit the function of effective T cells by increasing the secretion of IL-17A, IL-21, IL-22 and IL-26. In addition, Tregs could activate B cells and increase the infiltration of $CD8^+$ T cells, $CD38^+$ T cells and $CD39^+$ T cells, which restrains the antitumour activity of effective T cells. In addition, cancer cells could produce large amounts of FGL1 to inhibit effective T cell activation and then restrain antitumour responses. Additionally, CAFs could mediate the secretion of PGE-2, FAP, TGF-β, EGF, and VEGF to restrain the activity of NK cells and effector T cells. M1 macrophages are activated by IFN-γ, which is secreted by effective T cells, and efficiently produce inflammatory cytokines (IL-1, IL-6, IL-12 and TNF), which mediate resistance against cancer cells. M2 macrophages produce a mass of growth factors (EGF, TGF-β and VEGF) induced by TGF-β and IL-10, which restrain the activity of NK cells and effector T cells.

2.1. Tumour-associated macrophages (TAMs)

TAMs have a very important role in tumour-infiltrating immune cells within the TIME. TAMs can be classified into M1 and M2 subtypes via their polarization status and play two opposite roles in early tumourigenesis and tumour progression. Activated by Th1 cytokines (IFNγ) and microbial products, M1 macrophages perform an active role in the Th1 response and efficiently produce inflammatory cytokines (IL-1, IL-6, IL-12 and TNF), which mediate resistance against cancer cells and tumour progression [49]. In contrast, factors such as PGE2, transforming growth factor-β (TGF-β), macrophage colony-stimulating factor (M-CSF), and IL-10 give rise to M2 macrophages, which also respond to Th2 cytokines (IL-4, IL-10 and IL-13) [50,51]. M2 macrophages produce several growth factors (EGF, TGF-β and VEGF) for blood vessels, thus favouring the neoangiogenesis switch, tumour proliferation and invasion [52,53]. For CRC, the prognostic significance of TAMs is controversial and could depend on distinct phenotypes acquired at distinct localizations within the tumour [54]. Some studies have illuminated that high densities of TAMs favourably influence the postsurgical clinical outcome of CRC [55–57]. However, TAMs of CRC have also been found to secrete VEGF, thus facilitating angiogenesis and tumour metastasis [58]. A high density of TAMs in peritumoural liver tissue and peritumoural TAMs correlates with large tumour size, intrahepatic metastasis, and a poor survival of hepatocellular carcinoma (HCC) [59].

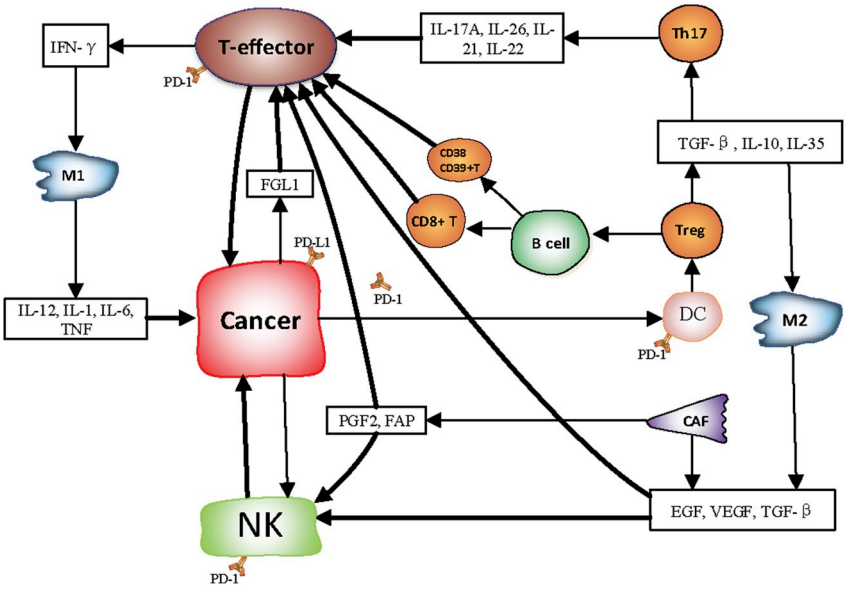

Fig. 1. The tumour immune microenvironment is depicted and shows the dynamic nature of the immune contexture of a tumour. Upon the recognition of tumour antigens, NK cells and DCs could be activated. NK cells could have an antitumour effect, while DCs could induce Tregs and increase IL-10, IL-35 and TGF-β secretion and then activate Th17 cells, which inhibit the function of effective T cells by increasing the secretion of IL-17A, IL-21, IL-22 and IL-26. In addition, Tregs could activate B cells and increase the infiltration of $CD8^+$ T cells, $CD38^+$ T cells and $CD39^+$ T cells, which restrain the antitumour activity of effective T cells. In addition, cancer cells can produce large amounts of FGL1 to inhibit effective T cell activation and then restrain antitumour responses. Additionally, CAFs can mediate the secretion of PGE-2, FAP, TGF-β, EGF, and VEGF to restrain the activity of NK cells and effector T cells. M1 macrophages are activated by IFN-γ, which is secreted by effective T cells, and efficiently produce inflammatory cytokines (IL-1, IL-6, IL-12 and TNF), which mediate resistance against cancer cells. M2 macrophages produce several growth factors (EGF, TGF-β and VEGF) induced by TGF-β and IL-10, which restrain the activity of NK cells and effector T cells.

2.2. Regulator T cells (Tregs)

As $CD4^+$ T lymphocytes, Tregs play vital roles in the TIME by producing suppressive cytokines (IL-10, IL-35 and TGF-β), inducing the cytolysis of antigen-presenting cells (APCs) and recognizing cell contact signalling (CTLA-4 and PD-1) to suppress the activation and proliferation of effector T cells [60–62], thereby contributing to tumour growth [63] and tumour immune evasion [64]. Generally, there are two major subsets of Tregs based on their source and phenotype. The first subset of Tregs is formed in the thymus and characterized by a $CD4^+CD25^+FOXP3^+$ ($FOXP3^+$ Tregs) phenotype, while the other subset is differentiated in the periphery and characterized by a $LAG3^+CD49b^+$ phenotype [65–67]. Some studies have shown that $FOXP3^+$ Tregs could suppress Th1 cytokine secretion and T cell proliferation to promote tumour growth and metastasis in CRC [68,69]. However, some studies have also reported a favourable prognostic outcome for high FOXP3+ Tregs in CRC [42,70,71], possibly because of the effect of bacterial translocation across the mucosal barrier in the colon [72,73]. Regulatory T cells, especially ICOS + FOXP3+ regulatory T cells, are increased in the HCC microenvironment and predict reduced survival [74]. The expansion of Tregs was found both in the peripheral blood and oesophageal mucosa of oesophageal cancer patients [75].

2.3. T helper type 17 (Th17) cells

Th17 cells are vital immune suppressive cells within the TIME that differentiate from naïve T cells under the activation of TGF-β and IL-6 [76,77]. Th17 cytokines, including IL-17A, IL-17F, IL-21, IL-22 and IL-26, can regulate oncogenesis and tumour progression [78,79]. Previous studies have reported that IL-17A, IL-17F, IL-21, and IL-22 are overexpressed in CRC patients [79–81]. More importantly, together with the activation of STAT3, Th17 cytokines can stimulate pathways that promote colorectal carcinogenesis and tumour progression [82,83]. Th17 cells can also promote tumour angiogenesis in CRC via IL-17-induced VEGF production, thereby accelerating colorectal tumour progression [41]. The accumulation of Th17 and Treg cells in the TIME gradually increased according to gastric cancer progression, and the imbalance in Th17/Treg cells was involved in the development and progression of gastric cancer [84].

2.4. Myeloid-derived stromal cells (MDSCs)

MDSCs are a group of immature cells comprising immature macrophages, myeloid progenitor cells, immature DCs and immature granulocytes derived from bone marrow. Monocytic MDSCs (M-MDSCs) and granulocytic MDSCs (G-MDSCs) are the two major subtypes of MDSCs [85,86], and they can expand during oncogenesis and restrain many kinds of T cell activities [87]. They can also differentiate into TAMs and secrete factors compensating for VEGF loss to support angiogenesis, thus promoting tumour progression [88]. MDSCs play a critical role in the immunosuppression mediation associated with CRC [89,90]. The expansion of MDSCs during chronic colitis resulted in an altered colonic microenvironment towards colorectal cancer development [91]. Moreover, MDSCs can enhance the levels of ROS and NO, which could induce DNA damage to promote tumour progression in CRC [92]. A previous study also found that MDSCs in circulation are associated with high tumour stage and lymph node metastases in CRC [93]. MDSCs, which were found to be increased in HCC patients, could augment Tregs, MDSCs, $PD\text{-}1^+$-exhausted T cells, and immunosuppressive cytokines (IL-10 and TGF-β1) in HCC patients. The depletion of Tregs, MDSCs, and $PD\text{-}1^+$ T cells restored effector T cell function in vitro [94].

2.5. B lymphocytes

B lymphocytes play an important role in acquired immunity, but historically, they have seemed to play an insignificant role in tumour immunity and cancer biology. However, several studies have revealed that B lymphocytes can take part in carcinogenesis and tumour progression by producing antibodies to facilitate chronic inflammation in the TIME [95–97]. Moreover, regulatory B cells can also restrain antitumour responses mediated by T cells in cancer [98,99]. Regulatory B cells, as a novel subsection of B lymphocytes, appear to play important roles in promoting tumour growth and progression via the production of IL-10 to suppress the activity of $CD8^+$ T cells in squamous carcinoma [98]. The presence of B cells in CRC seems to be associated with a poor prognosis [40,96].

2.6. Cancer-associated fibroblasts (CAFs)

Mostly derived from resident fibroblasts, CAFs are a vital source of cytokines (TGF-β, FGF2, VEGF, PDGF, etc.) and growth factors in the

TIME that promote tumour growth, angiogenesis and tumour progression [100–103]. In CRC, CAFs can mediate the secretion of PGE-2 to restrain the activity of NK cells and effector T cells, thus promoting colorectal carcinoma growth [32,104]. Furthermore, multifold factors derived from CAFs can mediate proliferative signalling in CRC and prompt colorectal tumour cells to escape growth suppressors and resist cell death [105]. Some studies have also shown that CAF-derived TGF-β and connective tissue growth factors facilitate the proliferation of CRC cells through the Smad 2/Smad 4 pathway [104,106,107]. Moreover, CAFs can secrete growth factors, thereby activating both the MAPK and PI3K/AKT pathways to mediate CRC cell proliferation, protein synthesis and invasion [108]. CAFs are important for cancer cell initiation and progression, and therapy targeting CAFs may be effective for treating fibrosis and preventing HCC progression [109].

3. The role of TIME in tumour immunotherapy and therapeutic resistance in GI cancer

Immunotherapy is one of the most important treatments in advanced solid tumours. After several decades of rapid development, it has been developed into several methods of treatment: tumour cytokines (interleukins, interferons, and thymosin), tumour vaccine treatment, cellular immunotherapy and immune checkpoint [24]. With the discovery of the TIME as an essential component of cancer, therapies targeting the TIME component have begun to be designed and applied in the clinic [25]. In Table 1, we summarize the factors affecting immunotherapy in the TIME. TIME of GI cancers, with its complex network of cells, cytokines, and chemokines, in tumour initiation, formation, growth, and metastasis affects outcome of current treatments [110]. In this section we mainly take CRC as an example to introduce strategy and mechanism of therapeutics resistance.

Immune checkpoint inhibitors have shown promising clinical results in MSI-H CRC [111]. By blocking the immune inhibitors CTLA-4 or PD-1/PD-L1, the natural host antitumour immune response is activated to eliminate a tumour and improve patient survival, even in advanced cancers. Thus, unlike chemotherapy, radiotherapy and targeted therapies, these immune checkpoint inhibitors work by ”releasing the brakes” to promote the host antitumour immune response [112,113]. Major breakthroughs have been made with immune checkpoint blockade therapy in several disease types, mainly including DNA mismatch repair-deficient/microsatellite instability-high (MSI-H) and high tumour-infiltrating lymphocyte (TIL) tumours; however, immune checkpoint monotherapy has not shown significant clinical success in the treatment of patients with mismatch repair-proficient (pMMR)/non-MSI-H CRC [114]. MSI occurs in 10–20% of gastroesophageal cancers and arises from deficient mismatch repair (MMR). MSI is highly correlated with nonsynonymous mutation burden as well as a dense accumulation of TILs [115].

Treatment resistance to tumours, including chemoresistance and immunotherapy resistance, can be grouped into two major categories: de novo resistance and acquired resistance. As a significant member of de novo drug resistance, environment-mediated drug resistance (EM-DR) is induced by multifaceted reciprocal crosstalk between tumour cells and their surrounding microenvironment [116,117]. The TIME comprises multifarious immune cells and extracellular components, which have great potential to modulate treatment resistance. Recent evidence has revealed TIME plasticity to be a determinant of treatment resistance in CRC [118,119].

3.1. Mechanisms of TIME-mediated therapeutic resistance

Two major categories of TIME-mediated therapeutic resistance have been prominently identified: cell adhesion-mediated drug resistance (CAM-DR), which is triggered by the attachment of tumour cells to the extracellular matrix or to the stroma, leading to resistance to antineoplastons by several signalling pathways, and soluble factor-mediated drug resistance (SFM-DR), which is mediated by chemokines, cytokines and growth factors within the TIME [24,117].

CAM-DR has been reported in various tumours. The extracellular matrix and some integrins, as well as their receptors, have been shown to participate in the process of CAM-DR. For instance, the mutual effects of tumour cells and the stroma via integrin and soluble factors lead to the stimulation of major survival pathways involving PI3K/Akt [120,121], accounting for tumour cell growth and drug resistance. Furthermore, β1 integrin-mediated PI3K activation overrides treatment-induced cell cycle arrest and apoptosis in many types of cancer, therefore promoting acquired resistance [122,123]. Previous studies have demonstrated the contribution of cancer-associated fibroblast-derived molecules to CAM-DR in CRC, such as type I collagen, which can restrain chemotherapeutic drug uptake in colon cancer cells [119]. Several studies also revealed that TAM abundance may induce CAM-DR in several tumour types [124–126].

Furthermore, a tremendous number of growth factors and cytokines within the TIME have been verified to be involved in SFM-DR tumours, which account for tumour cell growth, angiogenesis and drug resistance. For instance, SDF1 can regulate the activation of CXCR4, thus inducing resistance to cytarabine by downregulating the microRNA let-7a and promoting the transcriptional activation of MYC and BCL-XL in tumour cells [127]. CAFs can secrete hepatocyte growth factor to stimulate MET receptors and downstream PI3K/Akt signalling pathways, leading to intrinsic resistance to BRAF inhibitors [102]. Furthermore, TAMs can also promote cancer cell growth and therapeutic resistance by producing TNF-α and IL-6 [24]. Targeting pancreatic tumour cells alone appears unsuccessful to improve the prognosis of pancreatic cancer patients. The TIME of pancreatic cancer comprises several different cell types, including stellate cells, endothelial cells, nerve cells, immune cells (e.g., macrophages, lymphocytes, and dendritic cells) and the extracellular matrix [128]. In CRC, stromal cells within the TIME

Table 1
Summary of factors affecting immunotherapy in the immune microenvironment.

Factor	Description
TIL	The abundance of TILs can also be used as a marker to predict the efficacy of PD-1/PD-L1 blockade, which is usually achieved by immunohistochemistry to assess the infiltration of $CD8^+$ T cells in tumour tissue. A better response to the PD-1 antibody is observed in the peripheral blood of patients with $CD39^+$ $CD8^+$ T cells [13,112,113].
PD-L1	The amount of PD-L1 expression in tumour cells is also one of the indicators of predicting the drug response of the PD-1/PD-L1 antibody. The higher the PD-L1 expression, the better the anti-PD-1 drug efficacy [18,20].
Treg	As $CD4^+$ T lymphocytes, Tregs play vital roles in the TME by producing suppressive cytokines (IL-10, IL-35 and TGF-β), inducing the cytolysis of antigen-presenting cells (APCs) and recognizing cell contact signalling (CTLA-4 and PD-1) to suppress the activation and proliferation of T cells. A higher proportion of Tregs indicates a poor prognosis for tumour immunotherapy, and IFN-γ can enhance antitumour effects [58–73].
MDSC	MDSCs are a group of immature cells comprising immature macrophages, myeloid progenitor cells, immature DCs and immature granulocytes derived from bone marrow. A high proportion of MDSCs is usually observed in the blood of patients who do not respond to immunotherapy [83–92].
TAMC	TAMCs occupy a very important position in tumour-infiltrating immune cells within the TME. The prognostic significance of TAMCs is controversial. In general, a large number of myeloid cells (TAMCs) is a marker of a poor prognosis in tumour immunotherapy, and the efficacy of immunotherapy can be enhanced by inhibiting PI3K signals [50–57].

can facilitate resistance to oxaliplatin and 5-fluorouracil moderated through an SDF1/CXCR4-dependent mechanism in colorectal tumours [118].

3.2. Immune microenvironment and immunotherapy resistance

Primary immunotherapy resistance involves the intrinsic and extrinsic factors of tumour cells (Fig. 2). Intrinsic factors include the following: 1) the mutation frequency burden of abnormal genes, 2) the loss of tumour antigen expression, 3) the activation of protooncogenes (*EGFR, KRAS, MAPK, PI3K, WNT*, etc.), which leads to the intrinsic expression of PD-L1, 4) the tumour itself lacking effective antigen presentation, 5) the system itself lacking the expression of major histocompatibility complex (MHC), and 6) an abnormal mutation in the IFN-γ, MAPK, PI3K, and WNT signalling pathways, which results in the insensitivity of tumours to killer T cells. Extrinsic factors include the following: 1) the lack of killer T cell infiltration in the TME, 2) the abnormal activation of CTLA-4 and other immune checkpoints, 3) T cell exhaustion and phenotypic changes, and 4) the release of an immunosuppressive cell population (Tregs, MDSCs, and M2 macrophages) and the inhibition of the TIME by cytokines and metabolites (CSF-1, tryptophan metabolites, TGF-β, and adenosine) [6].

To our knowledge, the PD-L1/PD-1 pathway represents the archetypal tumour-adaptive immune escape mechanism. Upon the recognition of tumour antigens, tumour-specific effector T cells upregulate PD-1 and release IFN-γ, which induces PD-L1 in tumour and myeloid cells in the TIME. PD-L1 inhibits T cells through PD-1 engagement, interrupting antitumour T cell attack. This interruption of the antitumour T cell response represents a form of local immunodeficiency that allows tumours to escape and has been termed "adaptive immune resistance" [129–131]. Although T cells are the primary target of inhibition, as shown in many studies, the PD pathway could also impair the functions of DCs, macrophages, and NK cells [132–134]. PD-1-mediated suppression mechanisms include apoptosis, the induction of suppressive cytokines, anergy, exhaustion, and Treg induction [16,135]. How these potential mechanisms promote human cancer progression is currently being studied, along with possible new mechanisms.

Several underlying mechanisms may explain the immune resistance of pMMR/non-MSI-H mCRC to immune checkpoint inhibitor therapy, such as low TILs, low expression of tumour-specific antigens, a low mutation burden and the overexpression of intrinsic immunosuppressive factors in tumour microenvironment [6,7,136]. Recent studies have revealed that the activation of Wnt/β-catenin signalling is correlated with a reduction in intratumour T cell infiltration [8,9]. In general, the more $CD8^+$ T cells in tumour-infiltrating lymphocytes, the better the effect of tumour immunotherapy [12,16]. Studies in melanoma have found that activation of the Wnt signalling pathway is inversely correlated with the infiltration of $CD8^+$ T cells in tumour tissues. Additional analyses revealed that the activation of β-catenin signalling can inhibit the expression of the chemokine CCL4, thereby inhibiting the tumour infiltration of CD103 + DC cells, affecting the activation of $CD8^+$ T cells, and inhibiting $CD8^+$ and $CD4^+$ T cell-mediated antitumour immunity [8,137]. Therefore, this signalling pathway may play a role as an immune escape mechanism in CRC [10]. In addition, IFN-γ is generally produced by effector T cells in tumours or by APCs and recruits other immune cells to initiate antitumour proliferation and tumour-induced apoptosis effects [2,138]. Therefore, the IFN-γ signalling pathway is the central location of the antitumour effect. The mechanism is described in studies in which an inactivating mutation in the IFN-γ signalling pathway gene JAK1/2 can lead to acquired resistance to PD-1 blockade, and CD38 is a major mechanism of acquired resistance to the PD-1/PD-L1 blockade, causing $CD8^+$ T cell suppression [2,138].

A significant correlation between tumour mutational burden and the objective response rate to PD-1 inhibitors has been observed across cancers. GI cancers, such as hepatocellular cancer, oesophageal cancer, and gastric cancer, which have a lower rate of mutation burden than dMMR mCRC, show a 15–20% response to PD-1 inhibitors. Pancreatic cancer has a low mutation burden correlated with a poor response [139]. The analysis of tumour mutation burden in the TIME predicts the clinical benefit of immunotherapy.

In the latest study, it was demonstrated that fibrinogen-like protein 1 (FGL1) is an important functional ligand of lymphocyte activation gene 3 (LAG-3), and the role of the LAG-3-FGL1 pathway in tumour immunity was revealed. The same study revealed that FGL1 inhibits antigen-specific T cell activation, and blocking the interaction in the FGL1-LAG-3 pathway by monoclonal antibodies could stimulate tumour immunity. In addition, human cancer cells produce large amounts of FGL1, and the increased expression of FGL1 in cancer patients is associated with a poor prognosis and anti-PD-1/PD-L1 therapy. This study suggested that FGL1-LAG-3 is a new pathway for tumour immune escape and can be used as a potential target for tumour immunotherapy [140].

For CRC, with the definition of consensus molecular subtypes (CMSs) based on transcriptome profiles, multiple characteristics have been proposed to be responsible for the development of the tumour immune microenvironment and the corresponding mechanisms of immune escape [11,18]. CMS1 is characterized by MSI, a diffuse immune infiltrate composed of Th1 cells and CTLs, and a strong activation of immune evasion pathways; CMS2 tumours show high chromosomal instability and the activation of Wnt and MYC pathways; CMS3 displays frequent KRAS mutations and disrupted metabolic pathways, and CMS4 is characterized by the high expression of mesenchymal genes, stromal infiltration, angiogenesis and TGF-β activation. Among these four CMSs of CRC, each CMS has a differential prognosis, with CMS4 tumours displaying worse overall and relapse-free survival [11]. CMS1 and CMS4 tumours are characterized by high levels of immune infiltration, while CMS2 and CMS3 are devoid of immune cell infiltration. CMS1

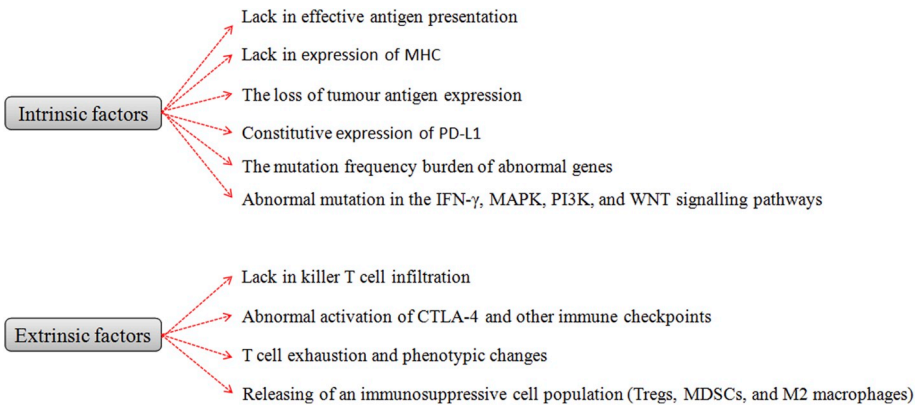

Fig. 2. Primary immunotherapy resistance involves the intrinsic and extrinsic factors of tumour cells.

tumours escape immune surveillance by upregulating oncogenes, while CMS4 tumours upregulate TGF-β, a potent immunosuppressive cytokine [3,11]. The low level of immune cell infiltration in CMS2 and CMS3 suggests a different mechanism of immune escape in these subtypes. The correlation between the upregulation of Wnt/β-catenin and T cells suggests that the failed recruitment of DCs is caused by the β-catenin-mediated suppression of CCL4 gene transcription, and this immune escape mechanism might also apply to CMS2 colon tumours [8].

3.3. Microenvironment-targeted strategies to improve the therapy response in CRC

Multiple approaches have been proposed to improve the therapy response in CRC based on the mechanisms of TME-mediated therapeutic resistance (Table 2). The feasible anti-EM-DR therapeutic targets include stroma-derived paracrine factors, tumour cell-extracellular matrix interactions and immune cells within the TIME, thus blocking pathways involved in EM-DR and restraining intricate interactions between tumour cells and the stroma to acquire durable treatment responses. A previous study illustrated that VEGF blockade upregulates inflammatory pathways and that NRP1 improves anti-VEGF therapy. For example, bevacizumab can upregulate stromal cell-derived factor 1A (SDF1A), as well as its receptors (CXCR4 and CXCL6), and downregulate PlGF, Ang 1, and Ang 2 in colorectal cancer cells. Furthermore, bevacizumab can also induce neuropilin-1 expression in TAMs [141].

Targeting IL-6 with specific receptor tyrosine kinase inhibitors has been proven to overcome EM-DR [142,143]. The IL-6 targeted approach has been proven to block stroma-derived IL-6, which is produced in response to tumour cells, and therefore disrupts the paracrine amplification loop [24]. Additional data have suggested that IL-6 released by colon cancer-associated fibroblasts can induce tumour angiogenesis by irritating nearby stromal fibroblasts. Anti-IL-6 receptor therapy can suppress angiogenesis and restrain the interaction between cancer cells and the stroma, which is crucial for improving the therapy response [144].

The effect on the immune system can be enhanced by combination with immune therapeutic approaches [145]. Several potential strategies for targeting the immunosuppressive activities of immune cells, including Tregs and MDSCs, within the TIME have been proposed [18,146]. Other targeted treatments focusing on TGF are also recommended for CRC, which are driven by the effect of the TGF-involved signalling pathway [147]. Antiangiogenic therapies by monoclonal antibodies against VEGF induce an adjuvant immune effect when combined with conventional chemotherapy [148]. For example, vandetanib is safely combined with cetuximab and irinotecan for metastatic colorectal cancer [149].

Tumour characteristics also play significant roles in improving the therapy response in CRC. Recent studies revealed that colorectal cancer with microsatellite instability (MSI) cannot benefit from adjuvant 5-fluorouracil therapy compared with tumours with microsatellite stability [150–153]. Triggered by deficient DNA mismatch repair mechanisms, MSI correlates with high levels of tumour-infiltrating lymphocytes and increased neoantigenic load [113]. Although immune checkpoint inhibitors have shown promising clinical results in several cancer types, immune checkpoint blockade responds in only a subset of CRC patients with high levels of MSI [112]. Colorectal cancer with MSI may be specifically targeted by immune checkpoint inhibitors because they are notably accompanied by an active TIME, which is characterized by the upregulation of immune checkpoint molecules, including CTLA-4, PD-1 and PD-L1 [154]. The latest research shows that there is a significant response to the PD-1 antibody in the peripheral blood of patients with $CD39^+$ $CD8^+$ T cells [13]. Therefore, there are several predictors that directly or indirectly relate to the immunotherapy response, such as the infiltration of $CD8^+$ T cells and $CD39^+$ T cells and the expression of PD-L1, Tregs, MDSCs, and TAMs.

3.4. Combination strategies and outlook to improve the therapy response in CRC

As a representative immune approach, PD-L1/PD-1 pathway blockade therapy has an inherent and significant advantage due to its broad therapeutic effect and minimal toxicity, which facilitate its use in combinatorial treatment. While combination therapy represents a popular, current strategy for the treatment of cancer, this strategy is largely driven by a mix of demands in clinical cancer care, corporate finance, market competition and scientific rationales. Over 1500 clinical trials that combine anti-PD therapy with nearly all available cancer therapeutics, including chemotherapy, radiotherapy, oncolytic viruses, targeted therapy, and other immunotherapies, are currently ongoing [130,155]. The majority of clinical trials are focused on the combination of anti-PD-1 with CTLA-4 as well as anti-PD-1 with chemotherapy [156]. As Table 3 shows, we summarize selected ongoing clinical trials for immnotherapy and these combinatorial approaches aim to overcome negative regulation of immnuo response in TIME.

Combined with chemotherapy, a previous study reported that PD-1 blockade showed better overall survival than single therapy in a short period of time (1–2 years) [157]. Chemotherapy or radiotherapy was reported to synergize with checkpoint inhibitors in combination therapy. Chemotherapy can increase antigenicity by inducing the immunogenic cell death of tumour cells and reducing immunosuppression in the TIME [158]. Local therapy is one method by which various biological and chemical agents are directly injected into tumours [159], including oncolytic viruses [160]. In experimental models, local therapies can induce tumour and distal tumour regression at the injection site. In clinical trials in which the local injection of an oncolytic virus in melanoma and brain tumours was performed, the reported results were promising [161,162]. Local therapies have been proven to be an effective way to increase TILs, which further improves the therapy response to PD-L1/PD-1 blockade [163].

The combination of immunotherapy and targeted therapy has a synergistic effect, which has been extensively explored in animal models and clinical trials [164,165]. Currently, there are a variety of immunotherapies under development that could be combined [166,167]. As a kind of immunotherapy, a tumour vaccine attacks tumour cells by inducing a specific immune function, overcoming the immunosuppressive state caused by tumours, enhancing the

Table 2
Summary of strategies to target tumour microenvironments to improve the therapy response.

Strategy	Description
Anti-EM-DR therapeutics	Target stroma-derived paracrine factors, tumour cell-extracellular matrix interactions and immune cells within the TME, thus blocking pathways involved in EM-DR and restraining intricate interactions between tumour cells and the stroma to acquire durable treatment responses [137–140].
Tumour characteristics	Some tumour characteristics, such as microsatellite instability (MSI), DNA mismatch repair deficiency (dMMR), PD-L1 expression, tumour-infiltrating lymphocytes (TILs), tumour mutation burden (TMB), and the infiltration of $CD8^+$ T cells and $CD39^+$ T cells, play significant roles in predicting the therapy response and guide individual treatment [13,109,110,146–150].
Combination therapeutics	The effect on the immune system can be enhanced by the combination of immune therapy and other approaches. Several potential strategies for targeting the immunosuppressive activities of immune cells, including Tregs and MDSCs, TGF and VEGF within the TIME have been conducted [141–145].

Table 3
Summary of recent clinical trials for immunotherapy in GI cancer.

Clinical trial identifier	Phase	Status	Start date	End date	Treatments	Targets	Study type	Target population	Arms	Sample No.
NCT03104439	II	Recruiting	2017.5	2020.10	Nivolumab, Ipilimumab, Radiation therapy	CTLA-4, PD-1	Single group assignment	Microsatellite stable colorectal cancer, pancreatic cancer, MSI high colorectal cancer	Nivolumab + Ipilimumab + Radiation therapy	80
NCT02448173	III	Recruiting	2015.5	2020.7	Oncovax and Surgery, Surgery		Randomized, parallel assignment, open label	Stage 2 colon cancer	OncoVAX and Surgery/Surgery	550
NCT01876511	II	Recruiting	2013.9	2021.6	MK-3475(an antibody that blocks negative signals to T cells)	PD-1	Non-randomized, parallel assignment, open label	MSI positive colorectal cancer, msi negative colorectal cancer, MSI positive non-colorectal cancers, High tumour mutation burden, high tmb	MSI Positive Colorectal Cancer/MSI Negative Colorectal Cancer/MSI Positive Non-Colorectal Cancer/MSI Negative with Mutator Phenotype	171
NCT01174121	II	Recruiting	2010.8	2023.12	Young til, aldesleukin, Cyclophosphamide, Fludarabine, Pembrolizumab (Keytruda)		Randomized, parallel assignment, open label	metastatic colorectal cancer, metastatic gastric cancer, metastatic pancreatic cancer, metastatic ovarian cancer, metastatic breast cancer		332
NCT03050814	II	Recruiting	2017.4	2020.8	Avelumab, Adcea vaccine, Bevacizumab, 5-fu, leucovorin, Oxaliplatin, Capecitabine	PD-1, VEGF	Randomized, sequential assignment, open label	Colorectal cancer	FOLFOX + Bevacizumab + Capecitabine/ FOLFOX + Bevacizumab + Capecitabine + Avelumab + Ad-CEA vaccine	97
NCT02614456	I	Recruiting	2015.12	2019.12	IFN-γ, PD-1 inhibitor Nivolumab	PD-1	Single group assignment, open label	Advanced solid tumours	IFN-γ and Nivolumab	15
NCT02900664	I	Recruiting	2016.8	2020.5	PDR001, ACZ885, CJM112, TMT212, EGF816	EGFR, EGFR T790 M mutation, PD-1, IL-1, IL-	Non-randomized, parallel assignment, open label	Colorectal cancer, triple negative breast cancer, nsclc - adenocarcinoma	PDR001 + canakinumab/ PDR001 + CJM112/ PDR001 + trametinib/	432

(*continued on next page*)

Table 3 (*continued*)

Clinical trial identifier	Phase	Status	Start date	End date	Treatments	Targets	Study type	Target population	Arms	Sample No.
						17, MEK, microsatellite stable			PDR001 + EG-F816/ canakinumab	
NCT02953782	II	Recruiting	2016.11	2020.5	Hu5f9-g4, cetuximab	CD47, EGFR, KRAS	Non-randomized, single group assignment, open label	Colorectal neoplasms	KRAS mutant/ KRAS wild-type: patients will receive Hu5F9-G4 in combination with cetuximab.	112
NCT02723955	I/II	Recruiting	2016.6	2020.5	gsk3359609(anti-Inducible T cell Co-Stimulator), pembrolizumab, docetaxel, pemetrexed, carboplatin, paclitaxel, gemcitabine, fluorouracil	PD-1	non-randomized, single group assignment, open label	cancer		500
NCT02904226	I/II	Recruiting	2016.8	2020.12	Jtx-2011, Nivolumab, Ipilimumab, Pembrolizumab	PD-1, ICOS	non-randomized, parallel assignment, open label	Cancer	JTX-2011/JTX-2011 + nivolumab/JTX-2011 + ipilimumab/JTX-2011 + pembrolizumab	498
NCT02994953	I	Recruiting	2017.1	2020.1	Avelumab, Nhs-il12, Avelumab (once weekly), Nhs-il12 (mtd), Avelumab (expansion cohort)	PD-1, IL-12	Non-randomized, sequential assignment, open label	Advanced solid tumours	Avelumab and NHS-IL12/ Avelumab (once weekly) + NHS-IL 12 (MTD)/ Avelumab (once weekly) + NHS-IL 12 (MTD) (Expansion cohort)	185
NCT02554812	II	Recruiting	2015.11	2020.12	Avelumab, Utomilumab, Pf-04518600, pd 0360324	PD-1, CD137, ALK, EGFR	Randomized, parallel assignment, open label	Advanced cancer		560
NCT03102047	II	Recruiting	2018.5	2019.12	Durvalumab, Chemo-radiation	PD-1	Single group assignment, open label	Rectal cancer with microsatellite stable	Durvalumab (Within 3 − 7 days after completion of chemoradiation, patients will receive Durvalumab every 2 weeks for 4 doses)	47

(*continued on next page*)

Table 3 (*continued*)

Clinical trial identifier	Phase	Status	Start date	End date	Treatments	Targets	Study type	Target population	Arms	Sample No.
NCT02837263	I	Recruiting	2016.8	2019.12	Stereotactic body radiotherapy (sbrt), Pembrolizumab	PD-1	Single group assignment, open label	Colorectal cancer	SBRT + Pembrolizumab	15
NCT02908451	I	Recruiting	2017.4	2020.10	AbGn-107(bifunctional fusion protein targeting PD-L1 and TGF-β)	AG7	Single group assignment, open label	Gastric cancer, colorectal cancer, pancreatic cancer, biliary cancer	AbGn-107 will be administered every 14-days or 28-days	116
NCT03122509	II	Recruiting	2017.5	2020.4	Durvalumab, Tremelimumab, Radiotherapy (rt), Ablation	CTLA-4, PD-1	Non-randomized, parallel assignment, open label	Metastatic colorectal cancer	Durvalumab and Tremelimumab plus Radiotherapy (RT)/ Durvalumab and Tremelimumab plus Ablation	33
NCT03184870	I/II	Recruiting	2017.8	2020.12	MS-813160, Nivolumab, Nab-paclitaxel, Gemcitabine, 5-fluorouracil (5-fu), Leucovorin, Irinotecan	PD-1, CCR2, CCR4	Non-randomized, parallel assignment, open label	Colorectal cancer, pancreatic cancer	Combination Therapy	348
NCT03841110	I	Recruiting	2019.2	2022.3	FT500(NK cell cancer immuno-therapy), Nivolumab, Pembrolizumab, Atezolizumab	PD-1	Non-randomized, parallel assignment, open label	Gastric cancer, colorectal cancer, pancreatic cancer		64
NCT02997228	III	Recruiting	2017.11	2022.4	Atezolizumab, Bevacizumab, Fluorouracil, Leucovorin calcium, Oxaliplatin	PD-1, VEGF	Randomized, parallel assignment, open label	Colorectal cancer, mismatch repair deficiency	Bevacizumab, mFOLFOX6/ Atezolizumab/ Atezolizumab, Bevacizumab, mFOLFOX6	347
NCT02912559	III	Recruiting	2017.9	2020.12	Atezolizumab, Ffluorouracil, Laboratory biomarker analysis, Leucovorin calcium, Oxaliplatin	PD-1	Randomized, parallel assignment, open label	Colon adenocarcinoma, dna repair disorder, lynch syndrome	Combination chemotherapy, Atezolizumab/ Combination chemotherapy	700

immunogenicity of tumour-associated antigens, and improving autoimmune power to eliminate tumours [168]. Approved by the FDA, an α-gal epitope-modified individualized tumour vaccine has been applied in clinical trials to prostate cancer, lung cancer, and melanoma and has potential application value for colorectal cancer [169]. Tumour cells were modified to an α-gal epitope-positive vaccine by α-1,3-galactosyltransferase, and an immune response similar to hyperacute rejection was induced. In this response process, tumour-associated antigens are efficiently presented and trigger the subsequent attack and killing effects of immune cells on the tumour in vivo [170]. The epithelial cell molecule Mucin 1 (MUC1), a transmembrane glycoprotein, is aberrantly overexpressed in various cancers, including CRC, and has been used as a candidate target antigen in peptides, dendritic cells, and whole tumour vaccines. Several clinical trials in progress have revealed the immunogenicity and suitability of MUC1, which acts as an immunotherapeutic vaccine for CRC [171]. To date, in the clinical trials of CRC, there is no report on the combination of a tumour vaccine and PD-L1/PD-1 blockade.

4. Conclusion

Tumour malignant progression and metastases have contributed to the high mortality of late-stage GI cancers, such as advanced CRC and HCC. In addition, increasing studies attribute a poor outcome to tumours characterized by the presence of MDSCs, B cells, Th17 cells and M2 macrophages within the TIME. Based on the knowledge that the TIME has a dynamic nature during malignant progression and resists immune reactions, multiple therapeutic strategies have been proposed to reverse TIME-mediated therapeutic resistance to restore the microenvironment favouring immune reactions, such as therapies targeted to inhibit Tregs, TAMs, and MDSCs. The combination of current immunotherapies to explore the synergy between vaccines and cytokines and checkpoint inhibitors or to adopt T cell transfer is also a viable approach. Moreover, targeted therapies that inhibit oncogenic signalling in cancer cells, such as the Wnt pathway and the EGFR pathway, are also under the development of combining immune therapeutic approaches. The TIME may represent a preferable approach to surmount drug resistance and improve the treatment response in GI cancers. However, the intricate reciprocities between GI cancer cells and the TIME during tumourigenesis and drug treatment still need to be investigated.

5. Author contributions

Yunbin Zhang prepared the figures and wrote the manuscript; Ning Zhang wrote the manuscript and prepared the tables; Jiang Xu, Ming Chen, Hua Wang edited the manuscript; Di Zhu contributed the idea, oversaw the process and wrote the manuscript.

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Conflicts of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors declare no competing financial interests.

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