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Review article

Immunotherapy in colorectal cancer: Statuses and strategies

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A B S T R A C T

Colorectal cancer (CRC) is widely recognized as the third most prevalent malignancy globally and the second leading cause of cancer-related mortality. Traditional treatment modalities for CRC, including surgery, chemotherapy, and radiotherapy, can be utilized either individually or in combination. However, these treatments frequently result in significant side effects due to their non-specificity and cytotoxicity affecting all cells. Moreover, a considerable number of patients face relapses following these treatments. Consequently, it is imperative to explore more efficacious treatment interventions for CRC patients. Immunotherapy, an emerging frontier in oncology, represents a novel therapeutic approach that leverages the body's immune system to target cancer cells. The principal advantage of immunotherapy is its capacity to selectively target cancer cells while minimizing damage to healthy cells. Its recent adoption as a neoadjuvant therapy presents significant potential to transform the treatment landscape for both primary resectable and metastatic CRC. This review endeavors to offer a comprehensive overview of current strategies in CRC immunotherapy, critically analyze existing literature, underscore anticipated outcomes from ongoing clinical trials, and deliberate on the challenges and impediments encountered within the field of immunotherapy.

1. Introduction

Cancer is a leading cause of mortality and represents a significant challenge to improving life expectancy worldwide. Colorectal cancer (CRC) is ranked as the third most frequently diagnosed malignancy globally and is the second most common cause of cancer-related deaths [1,2]. Colon cancer exhibits higher prevalence in North America, Europe, and Australia/New Zealand, whereas rectal cancer incidence is notably high in Eastern Asia. Conversely, the incidence rates of CRC are generally lower in most parts of Africa and South-Central Asia [3]. Notably, CRC incidence rates have demonstrated a consistent increase in regions undergoing rapid economic development, including Eastern Europe, Southeast Asia, South-Central Asia, and South America [4,5]. An emerging concern is the rising prevalence of CRC among individuals under the age of 50 [6].

CRC originates from the colon and rectum, beginning with the transformation of a normal colonic crypt into a benign intestinal polyp. Some adenomatous polyps can progress into advanced adenomas, which may eventually develop into malignant tumors capable of metastasis. However, the majority of polyps, including inflammatory and hyperplastic polyps, are not considered precancerous lesions [7]. Adenocarcinomas represent the most common type of CRC. The progression of CRC, termed "multi-step carcinogenesis", involves a series of progressive changes [8–10]. Three key molecular pathways have been identified in CRC carcinogenesis: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylation pathways (CIMP) [11]. Approximately 80 % of spontaneous CRC cases follow the CIN pathway, characterized by the classic adenoma-carcinoma sequence involving mutations in

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genes such as Kirsten rat sarcoma viral oncogene homolog (KRAS), adenomatous polyposis coli (APC), and tumor protein p53 (TP53). Mutations in APC are found in the majority (80–90 %) of both hereditary and sporadic CRC cases. These mutations disrupt the APC complex formation, leading to β-catenin translocation into the nucleus, hyperactivation of the Wnt signaling, and increased cell proliferation [9,12,13]. The development of cancer involves complex interactions among malignant cells, microenvironment components (such as stromal and vascular endothelial cells), and the immune system [14,15]. Consequently, the CRC microenvironment is characterized by intricate components and relationships, presenting significant challenges for therapeutic interventions.

Traditional approaches, such as surgical resection and chemotherapy, have long been considered the standard of care for CRC [16]. Despite efforts to raise public awareness for early CRC screening and advancements in cancer therapy, a considerable number of cases are diagnosed at advanced stages, contributing to the unfavorable prognosis of the disease [6,17]. For patients with unresectable lesions or those unable to undergo surgery, radiotherapy and chemotherapy remain key strategies for disease management. While radiotherapy can modulate the immune contexture of the tumor microenvironment and impact immunosurveillance, its efficacy in treating disseminated metastases is limited [16]. Recent studies have shown that chemotherapy in CRC patients, especially those with metastases, has improved their overall survival (OS), resulting in chemotherapy becoming the cornerstone of CRC treatment [18–20]. However, chemotherapy is associated with challenges such as systemic toxicity, variable response rates, and the development of resistance [21]. Despite the use of neoadjuvant or adjuvant chemotherapy or radiotherapy to reduce tumor burden, the prognosis for CRC, especially for patients with metastatic disease, remains unsatisfactory [6,22,23]. Therefore, the development of alternative and more effective treatments for CRC patients is imperative.

The mismatch repair (MMR)/microstatellite instability (MSI) system plays a pivotal role in the classification and therapeutic strategies for CRC. Microsatellites, comprised of repetitive nucleotide units, can undergo instability due to insertions or deletions in tumor cells, leading to frameshift mutations [24]. The MMR system, responsible for recognizing and repairing DNA damage, plays a critical role in correcting errors during DNA replication, including insertions, deletions, and mismatched bases [25]. The MMR system is categorized into mismatch repair deficiency (dMMR) and mismatch repair proficiency (pMMR). dMMR, characterized by the absence of MMR proteins, results in the accumulation of genetic errors and high instability (MSI-H) in tumor DNA. In contrast, pMMR indicates normal MMR protein expression and can be further subdivided into low instability (MSI-L) and stable (MSS) categories [26]. The dMMR/MSI-H subtype accounts for approximately 15 % of CRC cases and 5 % of metastatic CRC (mCRC) cases [27–30]. Due to the high mutation rate in dMMR/MSI-H tumors, they exhibit increased immunogenicity, activating the immune system against the tumor. Consequently, patients with dMMR/MSI-H show enhanced responsiveness to immune-based therapies, particularly immune checkpoint inhibitors (ICI) [31,32]. Hence, the exploration of novel and more effective immunotherapeutic strategies to address the diverse subtypes of CRC has become a primary focus of current research.

Immunotherapy has emerged as a promising and effective approach in cancer treatment by harnessing the patient's own immune system [33]. It has demonstrated remarkable success, particularly in melanoma and lung cancer [34], establishing it as a primary treatment modality for challenging solid tumors, including CRC [33]. In CRC immunotherapy, various strategies are being explored, including small molecule drugs, macromolecular drugs, cancer vaccines, adoptive cell transfer, and gene therapy [35]. Small molecule drugs target specific molecular markers on cancer cells, enhancing the immune response against them. Macromolecular drugs, such as immune checkpoint inhibitors, reinvigorate immune cells and unleash their antitumor potential. Cancer vaccines aim to stimulate the immune system through diverse approaches, such as peptide or protein-based vaccines, dendritic cell vaccines, or DNA/RNA-based vaccines. Adoptive cell transfer involves the infusion of expanded immune cells, such as T cells or natural killer cells, to enhance

Table 1
Overview of immunotherapies, their advantages and limitations.

Types of immunotherapies	Advantages	Limitations
Small molecule drugs	➢ It can be taken orally ➢ Low production cost ➢ Easy to store, easy to transport ➢ Better tissue permeability ➢ Broad spectrum ➢ Multiple mechanisms of action	➢ Off-target effect ➢ Low specificity ➢ Short half-life ➢ Prone to side effects
Macromolecular drugs	➢ Fewer side effects ➢ Longer half-life ➢ Better specificity ➢ Stronger interaction with proteins	➢ High production cost and complex production process ➢ Difficult to enter the cell ➢ Unstable
Adoptive Cell Therapy	➢ Individualized treatment for each patient ➢ Not limited by major histocompatibility complex ➢ Enhances individual immunity ➢ Better results in hematologic tumors	➢ Difficult expansion of immune cells and lack of persistence ➢ Toxic effects, such as cytokine disorders, neurotoxicity ➢ Immune cells cannot effectively infiltrate solid tumors ➢ Individualized cell therapy is costly
Cancer Vaccines	Shared advantages: ➢ Possess immune activating activity ➢ Capable of encoding the required antigens ➢ Well tolerated ➢ Almost with no dose-related toxicity	Shared limitations: ➢ Slow onset of action ➢ Potential safety hazards
Gene Therapy	➢ Higher targeting ➢ Non-cytotoxic ➢ Regulates the destructive nature of cancer cells	➢ May cause gene mutations ➢ The transfer rate and controllability of the target gene are not high ➢ Involves genetic intervention and raises ethical issues

the immune response against CRC. Gene therapy manipulates gene expression in either cancer cells or immune cells to augment antitumor activity. This comprehensive review provides an in-depth summary of CRC immunotherapy, encompassing various strategies and their underlying mechanisms. By evaluating both successes and limitations (Table 1), this review offers valuable insights into future research directions and the development of effective and personalized immunotherapeutic approaches for CRC treatment.

2. Small molecule drugs

Small molecule drugs have exhibited significant efficacy in targeting both extracellular and intracellular components, thereby

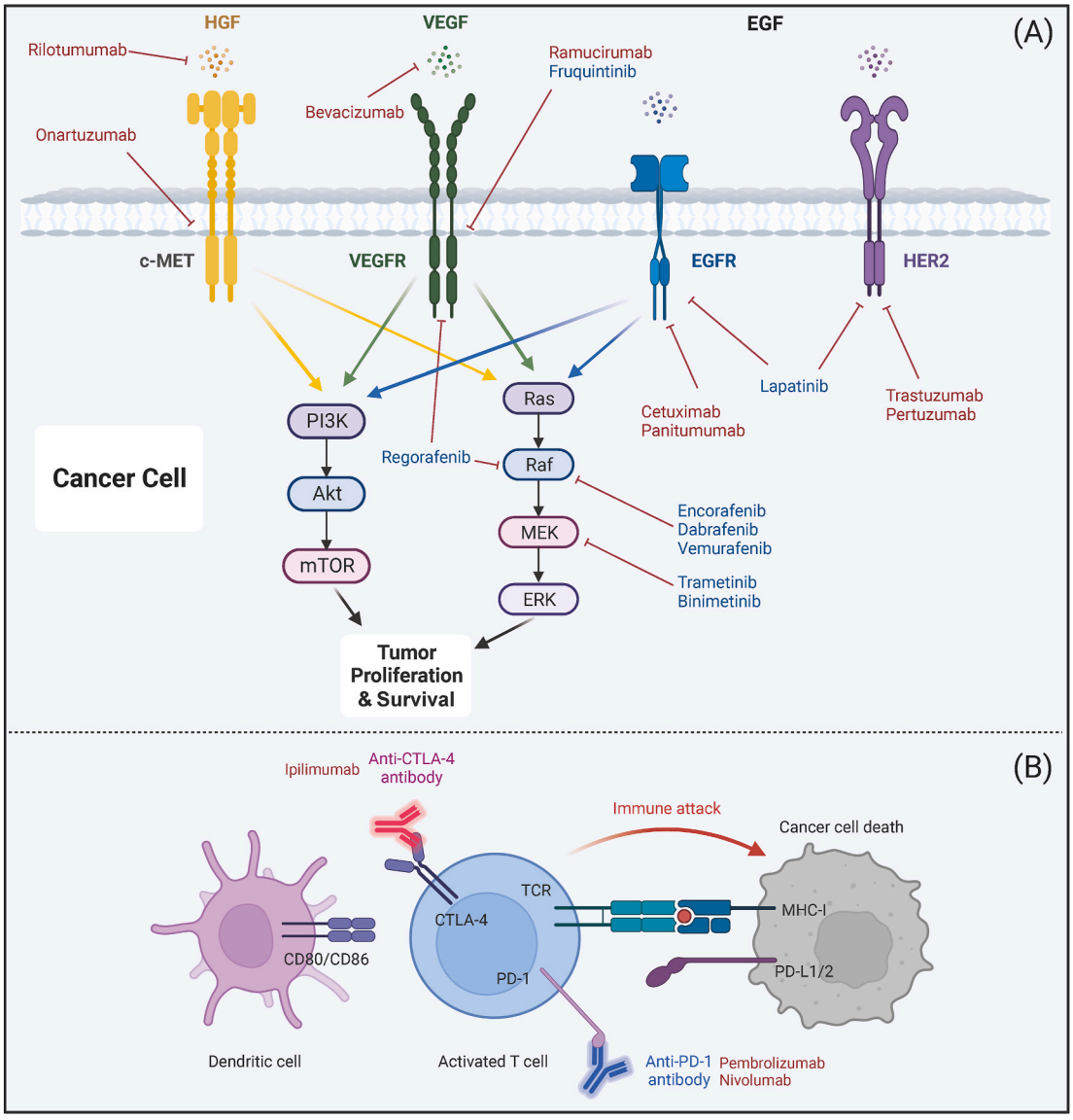

Fig. 1. Mechanisms of tumor target inhibitors and immunomodulatory mAbs. (**A**) Clinical utilization of targeted tumor inhibitors. This section illustrates targeted tumor inhibitors currently in clinical use. The inhibition of signaling pathways associated with cancer cell survival and growth leads to the death of cancer cells. Small molecule inhibitors are indicated in blue, while mAbs are indicated in red. (**B**) mAbs targeting immunomodulatory T cells. This section describes mAbs that target T cells, specifically anti-CTLA-4 and anti-PD-1. These mAbs counteract T cell suppression, thereby facilitating the release from immunosuppression and the subsequent elimination of cancer cells. Abbreviations: mAbs, monoclonal antibodies; HGF, hepatocyte growth factor; c-MET, mesenchymal–epithelial transition factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; HER2, human epidermal growth factor 2; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B, also known as PKB; mTOR, mammalian target of rapamycin; MEK, mitogen-activated protein kinase; ERK, extracellular signal regulated kinase. Created with BioRender.com.

modulating immune tolerance and suppression through molecular pathway alterations. This approach can elicit a robust antitumor response. By specifically manipulating key pathways and cells implicated in immune modulation, small molecules possess substantial potential to enhance the efficacy of cancer immunotherapy. The approval of imatinib, a small molecule tyrosine kinase inhibitor, in 2001 represented a seminal milestone in the development of small molecule drugs, heralding an exciting new chapter in the field of research.

2.1. Targeted tumor drugs

Specific small molecule drugs that target key pathways and receptors have demonstrated potential in the treatment of CRC (Fig. 1A). The epidermal growth factor receptor (EGFR), a member of the ErbB/HER family, activates intracellular signaling pathways such as RAS/RAF/MEK/ERK, PI3K/AKT, and JAK/STAT3, which are involved in regulating cellular growth, survival, and migration. In certain subgroups of CRC patients, EGFR and vascular endothelial growth factor receptor (VEGFR) inhibitors have successfully slowed disease progression, as observed in metastatic CRC (mCRC) [36] and rat sarcoma viral oncogene (RAS) wild-type mCRC patients [37]. Dysregulation of EGFR and human epidermal growth factor receptor (HER) expression is a common feature in various malignancies, rendering them potential therapeutic targets [38]. HER2 is particularly recognized as a significant therapeutic target in CRC. Recently, the FDA approved the use of pertuzumab and trastuzumab for treating adult patients with advanced RAS wild-type HER2-positive CRC [39]. The dual-targeting of HER2 and EGFR may offer increased efficacy compared to single-agent HER2-targeted therapy [40]. Angiogenesis-related factors, such as VEGF, fibroblast growth factors (FGFs), transforming growth factors (TGFs), platelet-derived growth factor (PDGF), and angiopoietins, play critical roles in tumor progression and resent potential targets for therapeutic intervention [41]. The hepatocyte growth factor (HGF), acting as an epithelial transition factor (MET) ligand, significantly contributes to tumor growth, survival, metastasis, and drug resistance [42]. Inhibition of the HGF-MET interaction could offer potential prognostic value in cancer [43].

Abnormal activation of tyrosine kinases, resulting from gene mutation, translocation, or overexpression, contributes to the tumorigenesis and progression of CRC. Although some tyrosine kinase inhibitors (TKIs) have demonstrated effectiveness in CRC patients, only a select few have received regulatory approval. Regorafenib, a multi-target TKI, has been shown to improve survival outcomes in patients with refractory mCRC [44]. Famitinib, which targets the c-KIT receptor, and fruquintinib, which inhibits VEGFR-1, 2, and 3, have also exhibited positive effects [45]. Cabozantinib, a broad-spectrum kinase inhibitor, has displayed promising antitumor activity in CRC models, whereas nintedanib has shown inconclusive benefits [45]. Further research is warranted to investigate the efficacy of newer agents, such as tepotinib, foretinib, glesatinib, and sitravatinib, in the treatment of CRC.

Small molecule drugs that target specific pathways and receptors offer promising therapeutic avenues for the treatment of CRC. However, the intricacy of signaling pathways and the propensity of tumor cells to develop resistance through diverse mechanisms pose significant challenges. To surmount these obstacles, the employment of combination therapies and the pursuit of further research into the mechanisms and antitumor effects of small molecule drugs are essential. By delving into the complex signaling networks that underlie CRC and elucidating the mechanisms of drug resistance, it becomes feasible to devise more targeted and efficacious treatment strategies aimed at enhancing patient outcomes.

3. Macromolecular drugs

Macromolecular drugs, particularly monoclonal antibodies (mAbs), have significantly influenced the field of oncology. Over the years, there has been a marked increase in the development and approval of mAbs for clinical applications, rendering targeted therapy with mAbs a pivotal strategy in cancer treatment (Fig. 1A). Innovative formats, such as bispecific antibodies and antibody-drug conjugates, exhibit substantial potential for the next generation of tumor-targeting therapies.

3.1. Monoclonal antibodies (mAbs)

3.1.1. Targeting tumor mAbs

Unlike polyclonal antibodies, which bind to multiple epitopes, monoclonal antibodies exhibit monovalent affinity, enabling their specific interaction with antigenic epitopes. mAbs can recognize and specifically bind to tumor-specific antigens (TSAs) or tumor-associated antigens (TAAs) present on the surface of cancer cells (Fig. 1). Cetuximab and panitumumab, monoclonal antibodies targeting EGFR, have demonstrated significant benefits in the treatment of mCRC [46,47]. Cetuximab has shown a positive impact on progression-free survival (PFS) in irinotecan-resistant patients, while panitumumab has been used as a first-line treatment, improving PFS and overall survival (OS) [48]. Both antibodies are recommended for CRC patients with specific mutations that typically confer lower response to anti-EGFR therapies. Another antibody, bevacizumab, which targets VEGF-A, has been approved for use in mCRC and enhances PFS and OS, despite associated adverse effects [49]. Ramucirumab, targeting VEGFR-2, when combined with FOLFIRI (Fluorouracil + Irinotecan + Leucovorin), has also shown improved OS. However, further evaluation is needed for its combination efficacy with other medications [50,51]. In contrast, inhibitors of HGF and MET have not demonstrated significant benefits in mCRC patients [52]. The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) presents a potential therapeutic opportunity, and selective DR5-binding monoclonal antibodies, such as conatumumab, have shown promise in preclinical tests and phase I trials [53]. Additionally, eftozanermin alfa, a TRAIL-R agonist, exhibits anticancer activity but requires further verification [54].

3.1.2. Immunomodulatory mAbs

Immunomodulatory monoclonal antibodies (mAbs) have emerged as potent cancer therapeutics due to their ability to inhibit tumor growth and augment the immune system's recognition of cancer cells. Immune Checkpoint Inhibitors (ICIs) represent a significant class of mAbs that target proteins involved in immune checkpoint pathways, predominantly expressed on T cells or various immune cell subsets. Prominent targets include Programmed Death receptor 1 (PD-1) and Cytotoxic T-Lymphocyte Antigen 4 (CTLA4), as depicted in Fig. 1B. In CRC, the efficacy of ICIs is substantially contingent upon the immune infiltration status of the tumors. Patients with tumors exhibiting dMMR or MSI-H, which are characterized by heightened lymphocyte infiltration, have been observed to have improved superior survival outcomes. Illustratively, a study documented a notably high 12-month overall survival rate of 73 % among such patients administered nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) [55]. In contrast, CRC tumors with MSS and pMMR typically display a diminished presence of immune cells and neoantigens, resulting in a subdued immune response. The FDA has granted approval for the anti-PD-1 antibodies pembolizumab and nivolumab for the treatment of MSI-H CRC [56,57].

While CTLA-4 inhibitors like Ipilimumab can counteract CTLA-4-mediated immunosuppression and promote T-cell activation, their clinical response in mCRC remains limited [58]. PD-1/PD-L1 inhibitors, such as pembrolizumab and nivolumab, restore effector T-cell function by disrupting the inhibitory signaling of PD-1 and its ligands. Although these inhibitors have demonstrated efficacy across various solid tumors [59], they confer more substantial benefits in CRC patients with dMMR or MSI-H, who exhibit significantly higher PFS rates compared to pMMR/MSS patients [30]. However, the therapeutic efficacy of both ICI monotherapy and combination therapy in mCRC, particularly in pMMR/MSS patients, still falls short of optimal outcomes [60,61]. Ongoing clinical trials are exploring dual immune checkpoint therapy for MSS patients, such as a combination of PD-L1 inhibitor and CTLA-4 inhibitor, but have not yet achieved improved treatment outcomes [62]. Ongoing investigations are focused on identifying new immune checkpoint targets, including T cell immunoglobulin domain and mucin domain-3 (TIM3), T cell immunoreceptor with Ig and ITIM domains (TIGIT), Lymphocyte Activation Gene-3 (LAG-3), and CD47, to expand the therapeutic options for CRC. These investigations hold promise for

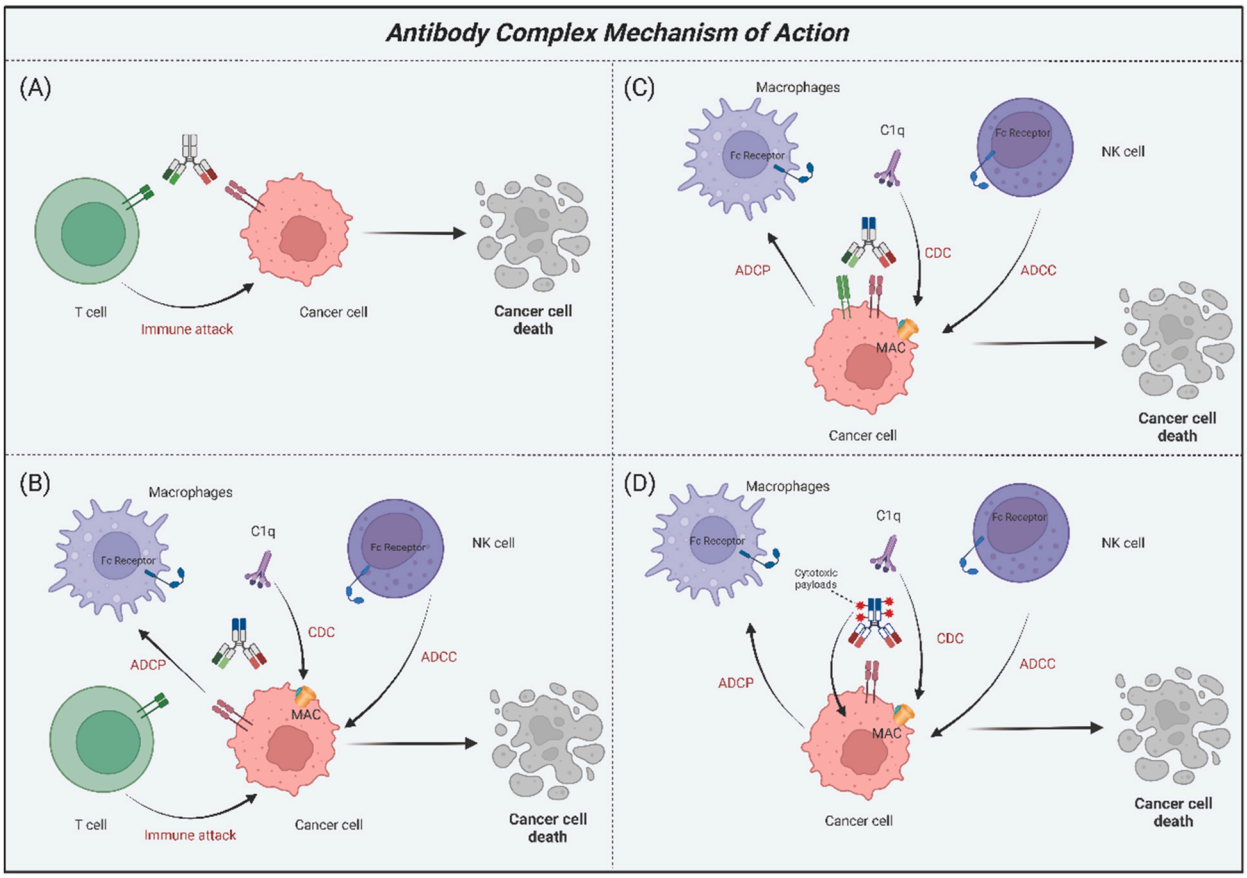

Fig. 2. Mechanisms of action of antibody complex. This figure illustrates the mechanisms of four distinct types of antibody complexes. (**A**) T cell recruitment. This class of antibodies facilitates the recruitment of T lymphocytes to target and attack cancer cells. (**B**) Enhanced immune responses. Beyond T cell recruitment, antibodies in this class possess Fc regions that mediate ADCC, ADCP, and CDC effects. (**C**) Dual cancer cell antigen targeting. Antibodies of this class are designed to target two distinct antigens on cancer cell, potentially enhancing their therapeutic efficacy. (**D**) Antibody-drug conjugates. These antibodies are capable of killing cancer cells by delivering a cytotoxic payload while also stimulating immune cells. Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; MAC, membrane attack complex, ADC, antibody-drug conjugates. Created with BioRender.com.

further enhancing treatment strategies for CRC patients.

3.2. Antibody complex

Monoclonal antibodies are characterized by their specificity to a single target, thereby conferring a singular biological effect. To mitigate unintended effects, it is essential in cancer therapy to concurrently disrupt multiple signaling pathways. Consequently,

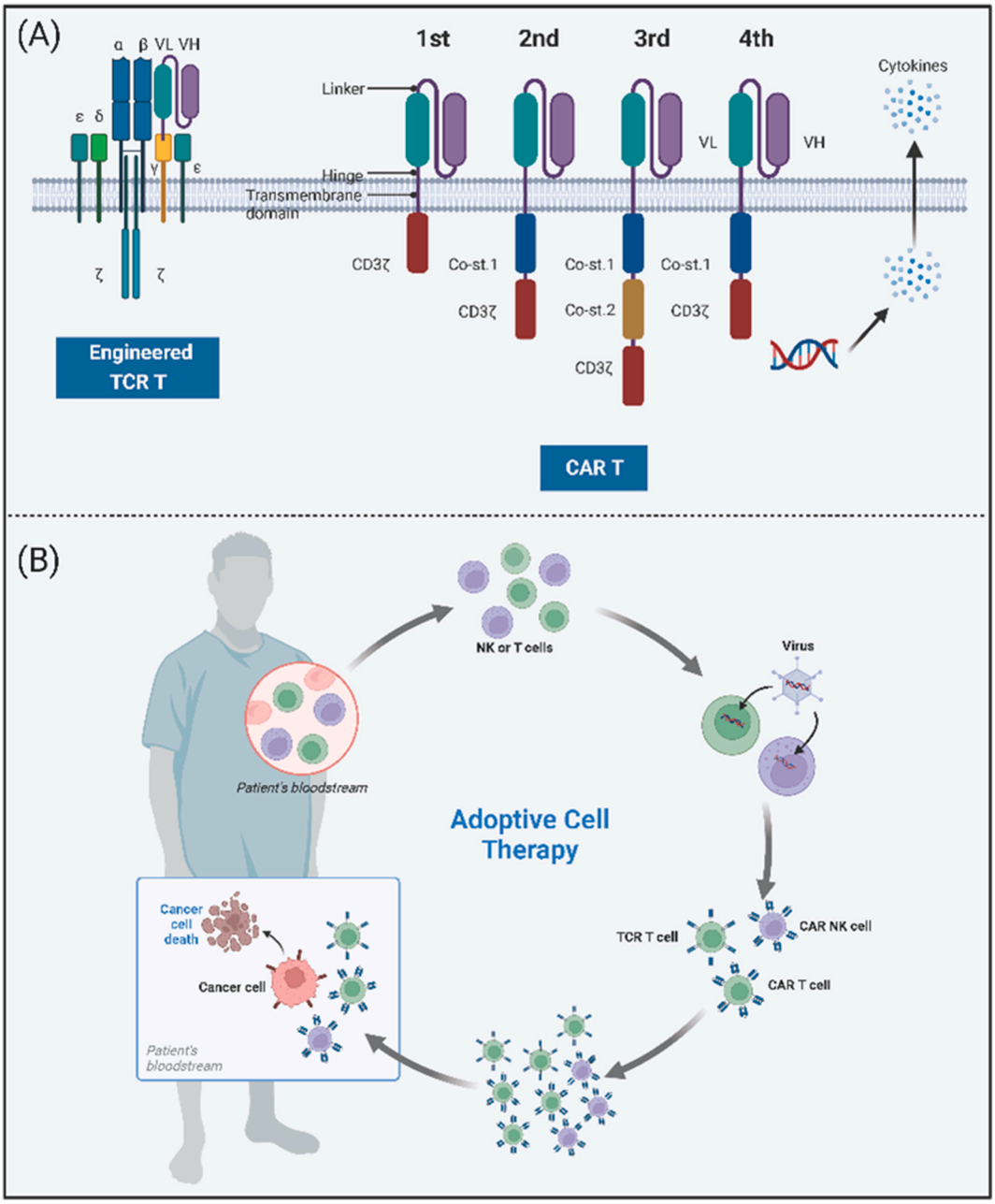

Fig. 3. Structure and therapeutic overview of adoptive cell therapy. (**A**) Architectural components. This section details the structure of T cells engineered with T cell receptors (TCR T) and each generation of CAR T cells. (**B**) Adoptive cell therapy procedure. **1**) Isolation: The patient's T cells or NK cells are isolated from their blood; **2**) Gene transfer: A viral vector is utilized to introduce the CAR-encoding gene into the T cells or NK cells; **3**) Expression: The modified T cells or NK cells express the CAR on their cell surfaces; **4**) Expansion: The CAR T cells, TCR T cells, or CAR NK cells are expanded in number; **5**) Reinfusion: The engineered cells are reintroduced into the patient's bloodstream; **6**) Targeting and elimination: The CAR T cells, TCR T cells, or CAR NK cells identify cancer cells expressing the target antigens and eliminate them. Abbreviations: TCR T, T cell receptor engineered T; CAR T, chimeric antigen receptor T; NK, natural killer. Created with BioRender.com.

bispecific antibodies (BsAbs) and antibody-drug conjugates (ADCs) offer enhanced benefits for the treatment of cancer (Fig. 2).

3.2.1. Bispecific antibodies (BsAbs)

Bispecific antibodies (BsAbs) represent a promising therapeutic approach for cancer treatment. These molecules possess the unique capability to recognize two distinct epitopes or antigens, thereby activating immune cells to target and eradicate tumor cells more effectively (Fig. 2A and B). Moreover, BsAbs have the capacity to concurrently inhibit signaling pathways associated with these disparate antigens (Fig. 2C). A notable subtype of BsAb is the bispecific T-cell engagers (BiTEs), which are recombinant proteins composed of two single-stranded variable fragments (scFv), devoid of the crystallizable fragment (Fc) region. Each scFv within a BiTE binds to either a T cell-specific molecule or a tumor-associated antigen, thereby facilitating robust T cell activation and enhancing the physical interaction between T cells and tumor cells.

Catumaxomab, a trifunctional antibody, targets three different cell types: tumor cells, T cells, and accessory immune cells, including macrophages, dendritic cells (DCs), and natural killer (NK) cells. It represents the first anti-EpCAM antibody to be approved for the treatment of malignant ascites in patients with EpCAM-positive tumors. However, caution should be exercised regarding its potential side effects [63]. Vanucizumab and duligotuzumab are other notable dual inhibitors, but their efficacy appears to be confined to specific subsets of CRC patients [64]. Bintrafusp alfa, a novel bifunctional fusion protein, inhibits immunosuppression and diminishes TGF levels within the tumor microenvironment [65]. Early clinical trials have demonstrated promising anticancer activity in patients who were previously considered untreatable [66].

3.2.2. Antibody-drug conjugate (ADC)

ADCs represent a novel class of anti-cancer treatments that combine the selectivity of monoclonal antibodies with the cytotoxic capabilities of chemotherapy agents. Upon binding to a specific antigen on cancer cells, ADCs are internalized into early endosomes, which mature into late endosomes and subsequently fuse with lysosomes (Fig. 2D). Within this compartment, the cytotoxic payload is released, triggering apoptosis in the cancer cell. As our understanding of ADCs advances alongside the development of new therapeutics, these conjugates are poised to offer significant potential in targeted cancer therapies. A notable example is cetuximab sarotalocan, an anti-EGFR ADC that demonstrates promising applications for the treatment of EGFR-expressing solid tumors, including CRC [67].

Immunotherapy utilizing mAbs has achieved significant advancements in the treatment of CRC. These mAbs demonstrate high selectivity due to their capacity to target specific antigens, positioning them as a vital therapeutic strategy for CRC. Combination therapies, which entail the simultaneous application of multiple therapeutic agents, have exhibited potential in augmenting the anticancer efficacy of macromolecular drug therapies. Despite the notable progress in macromolecular drug therapy for CRC, ongoing research and refinement are essential to maximize their effectiveness. Approaches such as personalized medicine, combination therapies, the discovery of novel targets, and the enhancement of immunotherapy response rates possess considerable potential to ameliorate treatment outcomes and yield superior clinical results for patients with CRC. Sustained endeavors in these domains will foster the evolution of CRC treatment, ultimately benefiting patients.

4. Adoptive cell therapy (ACT)

Adoptive immunotherapy presents a novel therapeutic approach for cancer treatment, harnessing immune cells such as T cells, DCs, NK cells, and cytokine-induced killer (CIK) cells. These cells, sourced from either the patient or a donor, are employed to stimulate an antitumor response in cancer patients (Fig. 3B). Among these strategies, T cell-based therapies have demonstrated the most significant promise, encompassing the utilization of tumor-infiltrating lymphocytes (TILs) and genetically modified T cells equipped with receptors intended to target the tumor, such as T cell receptors (TCRs) and chimeric antigen receptors (CARs). Although the FDA has granted approval for adoptive cell therapy (ACT) for a variety of hematologic malignancies, the majority of solid tumors remain in the clinical trial phase. This review is intended to provide a comprehensive discussion of the predominant cellular therapeutic approaches that are specifically tailored for the treatment of CRC.

4.1. Cytokine-induced killer (CIK)

Cytokine-Induced Killer (CIK) therapy represents an autologous form of adoptive immunotherapy, which entails the amplification of heterogeneous immune effector cells derived from peripheral blood mononuclear cells (PBMCs). CIK cells exhibit potent antitumor activity comparable to that of T lymphocytes, along with non-MHC-restricted tumoricidal properties akin to NK cells. Notably, CIK cells demonstrate robust recognition capabilities against tumor cells, functioning akin to “cellular missiles” that can precisely target tumor cells without affecting normal cells. They are especially efficacious following surgery or chemoradiotherapy, with the ability to eradicate residual micrometastases, prevent the dissemination and recurrence of cancer cells, and bolster overall immune function. Cell therapy products encompass conventional T cells ($CD3^+CD56^-$), NK-like T cells ($CD3^+CD56^+$), and NK cells ($CD3^-CD56^+$) [68]. CIK cells have demonstrated higher proliferation rates and more potent antitumor activity compared to other cell types, such as lymphokine-activated killer (LAK) cells and TILs, positioning them as a promising therapeutic option for solid tumors [68]. Research reports indicate that the proportion of the $CD3^+CD56^+$ subset increases in CRC patients following CIK cell therapy, and this increase correlates with improved OS and PFS in patients with mCRC [69,70]. A recent meta-analysis has revealed that patients who received additional CIK cell therapy achieved favorable outcomes without heightened toxicity compared to standard treatment, underscoring the necessity for further research into CIK therapy for CRC [71]. Nonetheless, optimizing cancer cell recognition in CIK therapy

necessitates additional investigation [72]. Specific subsets of CIK cells, including CEA-specific CAR-CIK cells and DC-CIK cells derived from the co-culture of DCs and CIK cells, are under exploration to augment therapeutic efficacy and avert tumor recurrence [73]. While promising, further clinical studies are warranted to ascertain the effectiveness of DC-CIK therapy [74]. Addressing limitations of CIK therapy, such as constrained migration capacity, may be accomplished through strategies like the use of CEA-specific CAR-CIK cells or the modification of chemokine receptor expression in CIK cells. Recently, a novel study discovered that functional CIK cells can be cultivated from patients with liver metastatic disease from CRC, advocating for continued investigation into the therapeutic application of autologous CIK cells in the management of CRC liver metastases [75]. Elucidating the signaling pathways implicated in CIK therapy can offer valuable insights for refining this treatment modality.

4.2. *Chimeric antigen receptor T (CAR-T)*

CAR-T cells have demonstrated significant efficacy in immune-targeted treatments for hematological cancers, which has led to FDA approval for these applications. Recent studies indicate promising progress in CAR-T cell therapy for CRC [76]. CARs consist of four critical components: the extracellular region (typically the Fab or scFv of a monoclonal antibody for antigen specificity), hinge structure, transmembrane domain, and intracellular signaling domain. CAR-T cell immunotherapy involves genetically modifying isolated peripheral blood T lymphocytes from patients to express CARs, enabling them to target specific antigens independently of MHC and antigen-presenting cells (APCs), proliferate through T lymphocyte expansion, stimulate cytotoxic T lymphocyte effector functions, and selectively kill cancer cells [77]. First-generation CARs had limited antitumor activity due to the absence of costimulatory signaling. Second-generation CARs integrated a costimulatory domain, such as 4-1BB or CD28, to enhance CAR function. Fourth-generation CARs further improved upon this by secreting cytokines such as IL-2 and IL-12 [78] (Fig. 3A). A novel development in CAR-T cells involves focused ultrasound and heat-inducible genes, enabling localized temperature control and enhanced CAR-T targeting [79]. While CAR-T cell therapy has achieved success in B-cell leukemia and lymphoma, advancements in solid tumors lag behind. The most studied targets for CRC in CAR-T cell therapy are CEA and NKG2DL, followed by EGFR and HER2 [80]. The first clinical trial of CAR-T cells targeting CRC began in 2014, evaluating the safety and efficacy of second-generation CEA-CAR T cells in CRC patients, as well as those with lung, gastric, breast, and pancreatic cancers (NCT02349724). Only two allogeneic CAR-T cell therapies specifically targeting CRC have entered clinical trials (NCT04107142 and NCT03692429), starting in 2019 and 2020, respectively [81]. Although a phase I trial in CRC showed stable disease in 70 % of CEA^{+} patients treated with CAR-T cells, challenges persist due to the short-lived presence of cells in the bloodstream and the occurrence of toxic reactions such as cytokine release syndrome (CRS) [82]. CRS typically occurs 1–14 days post-infusion, with variability based on CAR-T product, trial design, and patient population. Resolution of CRS usually occurs 2–3 weeks after CAR-T infusion [83]. Previous meta-analyses reported CRS incidence rates of approximately 55.3 % in patients with hematologic malignancies treated with CAR-T cell therapy, with severe CRS occurring in approximately 18.5 % [84,85]. Overcoming these challenges is crucial to fully harness the potential of CAR-T cell therapy for CRC treatment.

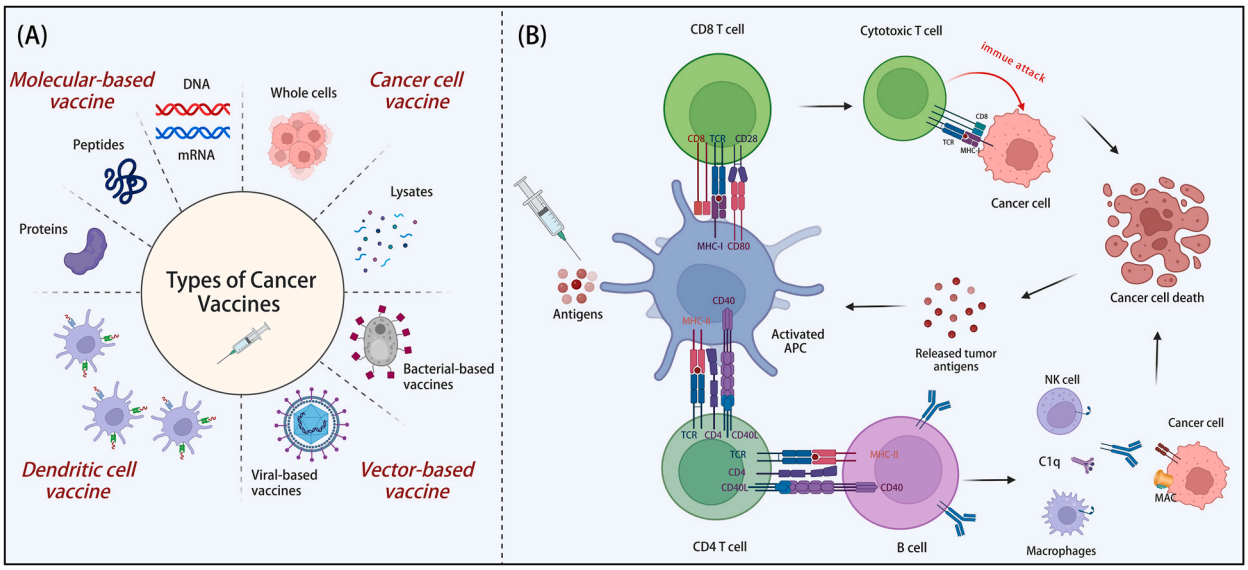

Fig. 4. Classification and mechanistic insights of cancer vaccines. (**A**) Types of cancer vaccines. This section outlines the various categories of cancer vaccines available. (**B**) Mechanisms of cancer vaccine action. DC vaccines: These vaccines employ DCs that are either loaded with tumor antigens ex vivo or transfected to express tumor antigens. Molecular-based and cancer cell vaccines: These types of vaccines stimulate the autologous APCs, leading to the activation of effector immune cells and the enhancement of an antitumor immune response. Abbreviations: MHC, major histocompatibility complex; TCR, T cell receptor; MAC, membrane attack complex; DC, dendritic cell; APC, antigen-presenting cell. Created with BioRender.com.

ACT, akin to many other therapeutic approaches, also has several limitations. The method presents significant technical and economic challenges for both the industry and patients, primarily due to the requirement of generating tumor-specific lymphocytes tailored for each individual. Furthermore, patients who receive allogeneic transplants are frequently at risk of developing graft-versus-host disease (GVHD). Additionally, toxicity is a major concern when targeting antigenic sites, such as TAAs, which are not only expressed in normal tissues but are also often overexpressed in tumors.

Cell therapy has emerged as a promising therapeutic strategy for the treatment of CRC, offering advantages such as high specificity, prolonged effects, and the ability to overcome drug resistance. Nevertheless, safety concerns, constraints imposed by the tumor microenvironment, and production-related challenges limit its widespread application. To address these limitations, improvement strategies include optimizing cell selection, enhancing treatment safety, and improving production efficiency while reducing costs. Cell therapy involves the preparation of cell "medicines" primarily in local production facilities. Obstacles affecting time-to-market and manufacturing costs include extended manufacturing durations, complex delivery systems, and decentralized, patient-specific production [86]. Although the wholesale acquisition costs for CAR-T cell therapy in treating B-cell lymphomas amount to $373,000, recent real-world studies by Prime Therapeutics indicate average total costs exceeding $700,000, potentially surpassing $1 million in certain cases [86]. The CRISPR/Cas system represents an efficient and straightforward method for precise gene editing, offering new possibilities for optimizing CAR-T cells by enhancing functionality and reducing manufacturing costs [87]. Efforts are actively evaluating numerous approaches to make ACTs more affordable, suggesting that this goal may soon become more than just an idealistic aspiration. Continued research and innovation in the field of cell therapy hold significant promise for achieving substantial breakthroughs in the treatment of CRC, thereby offering more effective and personalized therapeutic options.

5. Cancer vaccines

Cancer vaccines are formulated to elicit a robust immune response against tumor-specific antigens (TSAs), thereby targeting and eliminating cancer cells (Fig. 4). Since the discovery of tumor antigens in 1991, substantial advancements have been achieved in the domain of cancer vaccines. Over the intervening decades, there has been a sustained escalation in the number of clinical trials focused on CRC, concurrent with the emergence of innovative vaccine strategies. To date, the FDA has not granted approval for any CRC vaccines, with the majority remaining in the clinical trial phase.

5.1. Molecular-based vaccine

Molecular-based vaccines encompass peptide/protein, DNA, and mRNA vaccines (Fig. 4A). Protein-based vaccines possess multiple immunogenic sites that are amenable for processing and presentation by MHC I/II epitopes. However, despite phase II trials demonstrating the safety of vaccines when combined with oxaliplatin-based chemotherapy, no significant differences in treatment efficacy were observed [88]. Phase I trials of DNA vaccines have indicated both vaccine safety and the capacity to elicit an immune response by introducing gene sequences that encode tumor antigens [89]. In contrast, mRNA vaccines present significant advantages, such as high potency, ease of modification, shorter production time, and have shown clinical efficiency and safety in phase I trials. Promising mRNA vaccines, such as mRNA-4157, demonstrate potential [90].

5.2. Cancer cell vaccine

Cancer cell vaccines are formulated to stimulate the immune system by introducing either whole cancer cells or their lysates (Fig. 4A). These vaccines can be categorized as autologous or allogeneic based on the source of the cancer cells utilized. Autologous vaccines provide a high degree of specificity, while allogeneic vaccines offer the benefits of rapid production and broader applicability. However, the presence of antigens in normal tissues may elevate the risk of autoimmune responses. Encouraging results have been observed with vaccines such as OncoVax and GVAX, which have effectively enhanced antitumor immune responses. Further research is warranted to explore alternative vaccine strategies [91,92].

5.3. Dendritic cell vaccine

DC vaccines, which are induced to mature through cytokine culture, have exhibited promising outcomes in clinical trials for melanoma and prostate cancer [93]. MAGE-A3 is a tumor-associated antigen (TAA) that exhibits overexpression in CRC. The vaccine MelCancerVac has demonstrated promising potential for the treatment of CRC due to its targeting of the highly expressed MAGE-A3 [94]. Further investigation of the varying DC subpopulations is warranted to enhance vaccine development strategies [95].

5.4. Vector-based vaccine

Biological vectors, such as viruses, live attenuated bacteria, and yeast, can be genetically engineered to express cancer-specific antigens, thereby initiating immune responses. Vector vaccines primarily encompass viral vector vaccines and bacterial vector vaccines (Fig. 4A). Viral vector vaccines are recombinant and utilize viruses as carriers to deliver specific tumor antigens along with co-stimulatory molecules. These viral vectors possess inherent immunogenicity, functioning as adjuvants to enhance the induction of antitumor immune responses. Commonly used viral vectors include adenoviruses, fowlpox viruses, and vaccinia viruses. Adenovirus serotype 5 (Ad5)-based immunotherapy has been repeatedly employed in humans to induce robust T cell-mediated immune responses

while maintaining a high degree of safety [96]. Ad5 vaccines have demonstrated excellent safety and efficacy in treating mCRC [97]. PANVAC is a cancer vaccine therapy delivered via two viral vectors, recombinant vaccinia and recombinant fowlpox, and early clinical trials are assessing PANVAC both as a monotherapy and in combination with conventional chemotherapy and/or radiotherapy. Current research aims to establish PANVAC as a means to stimulate the immune system against malignant tumors and provide clinical benefits [98].

Oncolytic viruses (OVs) constitute an emerging approach in tumor immunotherapy, utilizing naturally occurring or genetically modified viruses that specifically infect and lyse tumor cells without harming normal cells. In addition to their direct oncolytic effects, OVs can induce immunogenic cell death and enhance antitumor immunity. Moreover, their toxicity profiles rarely overlap with those of other cancer therapies, which contributes to an acceptable safety profile [99]. Clinical trials are actively exploring the use of OVs in various solid tumors, including melanoma, glioma, and bladder cancer [100–102]. OVs offer new promise to the field of tumor treatment. Given their tolerable safety and unique antitumor mechanisms, combination strategies that integrate OVs with other therapies are demonstrating promising early clinical data [103].

Overcoming tolerance in the tumor microenvironment presents a significant challenge; therefore, considerable efforts have been dedicated to stimulating the immune system to generate robust responses against TAAs and TSAs [104]. Key characteristics of effective cancer vaccines include proficient antigen delivery, minimal impact on normal healthy tissues, and the capacity to elicit a strong antitumor immune response (Fig. 4B). In this context, Listeria monocytogenes, a facultative intracellular Gram-positive bacterium, serves as an attractive platform for cancer vaccine development due to its ability to activate tumor antigens and selectively deliver them to APCs, thereby generating potent antitumor cell-mediated immune responses [105,106].

Listeria-based vaccines have undergone extensive testing in numerous preclinical and clinical trials, targeting a spectrum of tumors including cervical cancer, melanoma, pancreatic cancer, breast cancer, prostate cancer, and malignant pleural mesothelioma [107–113]. Recently, a study on CRC indicated that a Listeria-based vaccination strategy, targeting the pericyte antigen RGS5, could elicit anti-angiogenic effects and trigger protective immune responses against colon cancer [114]. Similarly, Salmonella has been employed as a vector in CRC treatment. Recent research has shown that attenuated Salmonella strains delivering PD-1 small interfering (siRNA) can enhance the antitumor efficacy of EZH2 inhibitors in CRC [115]. It is essential to distinguish between bacterial immunogenicity and virulence during the production of recombinant vaccine vectors. Although substantial progress has been achieved in the development of cancer vaccines, their principal role seems to be as adjuvant therapies for patients with minimal residual disease or those in advanced stages of cancer. Further clinical research is warranted to evaluate their actual impact.

Cancer vaccination therapy offers several advantages, including high specificity, broad applicability, and a variety of vaccine types. However, challenges persist, particularly regarding immune tolerance and variability in treatment response. To augment the efficacy and practicality of CRC vaccinations, it is necessary to implement improvement strategies. These strategies include optimizing the selection of tumor-specific antigens, integrating multiple treatment modalities, personalizing vaccine formulations, and intensifying clinical research efforts.

In recent years, the combination therapy involving CAR-T cells and cancer vaccines has been extensively investigated across a range of cancer types. Reinhardt et al. discovered that a therapeutic approach targeting the tight junction protein claudin 6 (CLDN6), when combined with an RNA-lipoplex (RNA-LPX) vaccine encoding CLDN6, can significantly enhance the proliferation of CLDN6-specific CAR-T cells. This strategy has effectively eliminated human ovarian cancer and murine lung cancer cells in mouse models, as validated in both murine and human cancer cells [116]. Wang et al. developed CD19-CAR variants utilizing cytomegalovirus (CMV)-specific T cells. CAR-T cells engineered from CMV-specific T cells may exhibit sensitivity to CMV vaccination, potentially leading to the persistent proliferation of CAR-T cells in vivo. Furthermore, this strategy has been demonstrated to augment the measured antitumor capabilities in lymphoma-bearing mouse models [117].

Due to their high antigenic heterogeneity, cancers present significant challenges in the design of therapeutic cancer vaccines. RNA-based cancer vaccines have the capacity to encode newly mutated antigens for delivery, which contributes to their status as highly personalized medical products. However, this personalization is associated with high costs. These costs are driven by the expensive process of tumor sequencing and often necessitate complex logistics and the use of centralized sequencing facilities. One potential approach to reducing costs could involve the adoption of new decentralized third-generation sequencing technologies, which may offer improved cost efficiency.

6. Gene therapy

Genetic and epigenetic alterations are hallmarks of cancer progression. While chemotherapy is often effective, it frequently results in severe adverse effects. Targeted gene therapy presents a safer and more efficient treatment approach, aiming to improve patient survival and minimize disease recurrence. This therapy entails the introduction of new genes into cancer cells or adjacent tissues, inducing cell death or inhibiting the spread of cancer. It can be integrated with conventional therapies and utilizes targeted genetic approaches to enhance immune responses against tumors, facilitating the direct delivery of cytotoxic agents or genes to tumor cells. Over the past three decades, there have been significant advancements in cancer gene therapy, leading to the approval of several drugs and the initiation of ongoing clinical trials [118].

6.1. Targeting p53 and KRAS

CRC arises from the accumulation of genetic and epigenetic alterations that disrupt signaling pathways regulating cancer. Six key driver genes in CRC have been identified: APC, KRAS, B-Raf proto-oncogene, serine/threonine kinase (BRAF), Phosphatidylinositol-

4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), SMAD family member 4 (SMAD4), and TP53 [119]. Gene therapy targeting the p53 gene is being explored for various solid tumors, with the aim of inhibiting mutant p53 function and halting CRC progression. Gendicine, the first gene therapy product for head and neck squamous cell carcinoma (HNSCC), has demonstrated tumor suppressor activity by restoring wild-type p53 expression, leading to cell cycle arrest, DNA repair, or programmed cell death in response to cellular stress. Other targeted gene therapies, such as Rexin-G for pancreatic cancer and VB-111 for glioblastoma, have shown promise [120,121]. In contrast, KRAS-targeted gene therapies are still underdeveloped, despite indications of potential efficacy. The KRAS gene is one of the most commonly mutated oncogenes, accounting for approximately 40 % of all CRC cases when mutated [122]. RAS proteins are small membrane-associated GTP-binding proteins that participate in multiple signaling pathways, ultimately regulating cell growth, motility, angiogenesis, and survival in various cancer types [123]. These mutations can lead to the permanent activation of KRAS, resulting in uncontrolled cell growth and proliferation. The downstream signaling pathways activated by mutated KRAS involve a complex network of proteins that promote cell proliferation and survival, which are associated with tumor progression and resistance to targeted therapies [124].

Recommended treatment regimens for KRAS-mutated CRC include fluoropyrimidine-based therapies in combination with oxaliplatin and/or irinotecan, as well as the incorporation of anti-VEGF therapies in both first- and second-line treatments [125]. Clinical efficacy has been observed with the use of KRAS G12C inhibitors, such as adagrasib and sotorasib, in previously treated patients with various tumor types, including CRC [126,127]. Currently, the KRYSTAL-10 trial is a randomized Phase III study comparing the combination of adagrasib with cetuximab against chemotherapy. This trial has completed patient recruitment and is awaiting results in

Table 2
Summary of clinical studies on immunotherapy for CRC from January 1, 2023, to August 11, 2024, as indexed on PubMed.

No.	Drug name	Target	Immunotherapy type	ClinicalTrials.gov identifier	CRC type	References
1	ELI-002 2P	G12D and G12R mutant KRAS	Cancer vaccine	NCT04853017	CRC	Pant et al. [131]
2	Nivolumab plus Ipilimumab	PD-1	Monoclonal antibody	NCT03026140	dMMR CRC	Chalabi et al. [132]
3	Bevacizumab	anti-VEGF-A	Monoclonal antibody	NCT03950154	mCRC	Pan et al. [133]
4	Divarasib plus Cetuximab	KRAS G12C	Monoclonal antibody	NCT04449874	KRAS G12C	Desai et al. [129]
5	Oleclumab	CD73	Monoclonal antibody	NCT02503774	Advanced CRC	Bendell et al. [134]
6	Nivolumab and Metformin	PD-1	Monoclonal antibody	NCT03800602	MSS CRC	Akce et al. [135]
7	PexaVec	/	Oncolytic viruses	NCT03206073	pMMR CRC	Monge et al. [136]
8	Camrelizumab	PD-1	Monoclonal antibody	/	pMMR CRC	Li et al. [137]
9	Personalized neoantigen vaccine	/	Cancer vaccine	/	MSS CRC	Yu et al. [138]
10	T-VEC	/	Oncolytic viruses	/	CRC with liver metastases	Hecht et al. [139]
11	Nivolumab	PD-1	Monoclonal antibody	NCT03414983	mCRC	Lenz et al. [140]
12	Pixatimod	TLR9		NCT05061017	MSS CRC	Lemech et al. [141]
13	NIS793	TGF-β	Monoclonal antibody	NCT02947165	MSS CRC	Bauer et al. [142]
14	MUC1Peptide Vaccine	MUC1		/	Colorectal Adenoma	Schoen et al. [143]
15	Durvalumab and Tremelimumab	PD-L1 CTLA-4	Monoclonal antibody	/	mCRC	Loree et al. [144]
16	Durvalumab	PD-L1	Monoclonal antibody	NCT04083365	Advanced CRC	Grassi et al. [145]
17	Monalizumab plus Durvalumab	NKG2A/CD94 and PD-L1	Monoclonal antibody	NCT02671435	MSS CRC	Patel et al. [146]
18	PD-1 blockade plus COX inhibitors	COX and PD-1	Monoclonal antibody	NCT03638297	dMMR mCRC	Wu et al. [147]
19	Enadenotucirev	/	Adenoviral vector	NCT02636036	MSI-low/MSS CRC	Fakih et al. [148]
20	Urelumab	CD137 agonist	Monoclonal antibody	NCT02110082; NCT02253992	mCRC	Khushalani et al. [149]
21	VB-111	Tumor microenvironment	Adenoviral vector	NCT04166383	MSS CRC with liver metastases	Coffman-D'Annibale et al. [150]
22	hTERT	/	Vaccination	/	CRC	Zareian et al. [151]
23	Cibisatamab	CD3 and CEA	Bispecific antibody	NCT02324257 NCT02650713	MSS CRC	Segal et al. [152]
24	TERTiNTs	4-1BB	Cell therapy	/	CRC	Choi et al. [153]
25	NEO-201	CEACAM-5/6	Monoclonal antibody	NCT03476681	CRC	Cole et al. [154]
26	Sapanisertib	mTORC1/2	Monoclonal antibody	/	CRC	Coleman et al. [155]

the coming months.

Additionally, novel KRAS inhibitors, such as divarasib and garsorasib, have demonstrated significant clinical activity, achieving disease control rates of 84 % and 95 %, respectively, in monotherapy. They have also shown considerable clinical activity when used in combination with anti-EGFR therapies. Specifically, when divarasib is used in conjunction with cetuximab, the disease control rate can increase to 95.8 % [128,129]. However, despite the promising data from these trials, careful interpretation is essential due to the small size and the non-randomized nature of the Phase I and II clinical trials. Therefore, standardized treatment regimens involving p53 and KRAS gene therapy require further development and rigorous evaluation.

Gene therapy for CRC offers several advantages, including high specificity, safety, and a diversity of approaches. However, it faces significant challenges due to technological limitations and variability in treatment effectiveness. To date, the FDA has approved a total of 19 gene therapies, many of which now include the first CRISPR genome editing therapy for sickle cell disease, CASGEVY. This therapy is currently the most expensive drug on the market, with a price tag exceeding $4 million per patient. Jennifer A. Doudna has proposed a pricing structure that, once implemented, could potentially reduce costs per patient by an order of magnitude and has suggested a business model that allocates responsibility while leveraging diverse funding sources [130]. By enhancing gene delivery efficiency, integrating multimodal therapies, implementing personalized treatment strategies, and advancing clinical research, the efficacy and feasibility of gene therapy for CRC can be significantly improved.

7. Future directions

Given the escalating global prevalence of CRC, there is an urgent need to develop superior treatment options for advanced and metastatic disease. Immunotherapy has demonstrated promising responses in a significant number of CRC patients, improving patient survival, minimizing adverse effects, and in some cases, facilitating complete recovery. However, a fundamental challenge is overcoming primary resistance to immunotherapy, which is prevalent among the majority of CRC patients. Potential mechanisms of resistance in CRC encompass downregulation of tumor antigen presentation, loss of T cell functionality in the host, and the emergence of mutant variants enabling cancer cells to evade immune surveillance. Combination therapy, targeting multiple pathways, is regarded as the most potent antitumor strategy. Various pathways are being targeted using a combination of multiple drugs, increasing the likelihood of arresting disease progression. This therapeutic approach can effectively tackle tumor heterogeneity, enhance treatment efficacy, and counteract drug resistance, thereby aiding in the eradication of cancer stem cells (Table 2).

Emerging tools, such as nanotherapies that leverage specific characteristics of the TME, offer novel avenues for immunotherapy. When nanotherapies are used in combination with other tumor-targeted therapeutics, they have demonstrated superior outcomes compared to single-targeted agents. Numerous studies have confirmed that nanoparticle-mediated, TME-targeted antitumor therapies exhibit potent immunosuppressive effects and hold potential for treating tumors when used in conjunction with other therapeutic approaches [156]. Recent advancements in computational analysis and artificial intelligence (AI) have deepened our understanding of the TME. By integrating and analyzing complex molecular data from immune cells, stromal cells, and other components of the TME, AI and computational biology can elucidate the molecular mechanisms underlying the TME and its pathological outcomes. While questions regarding their reliability and accuracy persist, the widespread application of these techniques and their potential as effective adjuncts to tumor immunotherapy are anticipated to expand as the technology matures.

CRediT authorship contribution statement

Yuan Li: Writing – original draft, Visualization, Investigation. **Zewei Cheng:** Writing – original draft, Visualization, Data curation. **Shengli Li:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Jiwei Zhang:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

Declaration

We confirm that this manuscript is not under consideration elsewhere and that all authors have consented to its submission.

Data availability statement

No data were utilized in the research presented within this article.

Ethics approval and consent to participate

Not applicable. This article contains no studies performed by authors with human participants or animals. It is a comprehensive review, synthesizing insights from previously published articles.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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