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Mini Review

Current Advances in Immunotherapy for Colorectal Cancer

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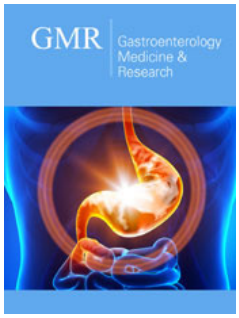
ISSN: 2637-7632



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Submission: June 26, 2024
Published: July 05, 2024

Volume 7 - Issue 5

How to cite this article: Li Ma, Stefan Moisyadi and Wen-Ming Chu*. Current Advances in Immunotherapy for Colorectal Cancer. Gastro Med Res. 7(5). GMR. 000675. 2024.
DOI: 10.31031/GMR.2024.07.000675

Abstract

Purpose: This study aimed to briefly review the current advances in immunotherapy for colorectal cancer.

Methods: We conducted a brief review of the latest literature.

Results: We discuss the advantages and challenges of variable forms of immunotherapy for colorectal cancer

Conclusion: Immunotherapy holds great promise for colorectal cancer.

Keywords: mRNA; Immunotherapy; PD-1; PD-L1; Monoclonal antibody (mAb); Nanobody (Nb); CAR-T; CAR-NK; Colorectal cancer; TME

Introduction

Colorectal Cancer (CRC) is the third most common cancer in the United States1. Although the incidence of CRC has been reduced in people over 55 years old, it has markedly increased in those under 55 years old [1]. In the early-stages, CRC usually shows no symptoms and is difficult to identify. Once it is diagnosed, the majority of CRC have already become metastatic CRC (mCRC) leading it to being the second leading cause of cancer-associated death in the United States [1]. Therefore, there is an urgent need for better therapeutic strategies for the disease. Cancer immunotherapy has transformed CRC treatment by harnessing the innate capabilities of the host immune system to combat and eliminate cancer. Cancer immunotherapy has come in a variety of forms including immune checkpoint inhibitors, cancer vaccination and immune cell therapy.

Immune checkpoint inhibitors are monoclonal antibodies (mAbs) targeting programmed death-1 (PD-1), PD-1 ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4). The PD-1 mAb has been approved by the Food and Drug Administration (FDA) as the first-line treatment and anti-PD-L1 mAb as the second-line treatment for mCRC. However, only 5% of mCRC patients respond to anti-PD-1 therapy. These mCRC patients harbor mutations in mismatch repair genes leading to high microsatellite instability (MSI-H) and the accumulation of somatic mutations. The somatic mutations are found in about 15% of CRC patients causing the expression of neoantigens. These neoantigens are perceived as foreign by the body triggering adaptive immune responses and subsequent tumor infiltration of innate immune cells and T cells and their expression of immune checkpoint molecules in the Tumor Microenvironment (TME) of "hot CRC". Conversely, approximately 85% of CRC cases exhibit low microsatellite instability (MSI-L) or Microsatellite (MSS), characterized by the absence of tumor-infiltrating innate immune cells and T cells, as well asl the lack of immune

checkpoint expression on these cells in the TME of "cold CRC". Moreover, there are abundant Myeloid Derived Suppressor Cells (MDSCs) and Tumor-Associate Macrophages (TAMs) in the TME of cold CRC, impeding the effectiveness of anti-PD-1 and anti-PD-L1 therapy. Furthermore, mAbs are large molecules and have limited tumor penetration capacity diminishing therapeutic efficacy of anti-PD-1 and anti-PD-L1 therapy for mCRC.

Nanobodies (Nbs) and single-chain variable fragments (scFvs) derived from IgG of monoclonal antibodies targeting immune checkpoints are small molecules characterized by low immunogenicity and the ability to efficiently penetrate tumor tissues [2-4]. They are excellent alternatives for treating CRCs. However, these Nbs and scFvs have a short serum half-life hindering their anti-CRC immunity capabilities. A strategy of fusing a Nb with Fc fragment of IgG that increases the size and slows down the renal clearance rate has been successfully used to generate a recombinant PD-L1Nb-Fc (KN035-Fc), which has been approved to treat MSI-H solid tumors including mCRC with frequent administrations [5,6]. The cell immunotherapy via modified T cells, chimeric antigen receptor-T (CAR-T) cells and CAR-natural killer (CAR-NK) cells has been used to treat CRC in pre-clinical and clinical trials. Typically, patients' own T cells or NK cells are transduced by lentiviral particles containing CAR DNA constructs which selectively target and eliminate tumors. Research findings indicated that a patient with MSI-H mCRC, who developed resistance to the PD-1 inhibitor pembrolizumab, achieved stable disease survival for six months following treatment with T cell receptor-(TCR)-redirected T cells targeting mutant transforming growth factor beta receptor 2 [7]. Pre-clinical and clinical trials using a CAR-T or a CAR-NK strategy to treat mCRC have recently been reported or reviewed elsewhere [8,9]. However, while engineered CAR-T cells have cured patients with untreatable hematological cancers, the CAR-T therapy faces challenges with poor cell penetration into solid tumors, cytokine release syndrome (CRS), 'on-target, off tumor toxicity' and genotoxicity [10].

Messenger RNA technology has emerged as a powerful platform that enhances the effectiveness of immunotherapy. Lipid Nanoparticles (LNPs) encapsulating *In Vitro* Transcribed (IVT), nucleoside-modified (N1-methylpseudouridine-containing) mRNA vaccines against COVID-19 have proven to be a promising and highly successful approach in mitigating the severe impacts of the COVID-19 pandemic. This IVT mRNA-LNP technology has rapidly integrated into immunotherapy forming the platform of mRNA vaccines, mRNA-driven production of mAbs, Nbs and proteins of interest, and mRNA-associated CAR-T and CAR-NK cell therapy. This platform provides standardized procedures within well-equipped facilities, efficiently delivering mRNA into cells to avoid genotoxicity and reduce immunogenicity and potential Cytokine Release Syndrome (CRS). It also enables rapid and continuous production of monoclonal antibodies, nanobodies, and proteins either in cells or *in vivo* [10-12]. For example, once a tumor associated protein or a specific antigen is identified from tumors, an mRNA construct is quickly engineered and then is used either to transfect Dendritic Cells (DCs) producing DC vaccines or to be delivered directly to the host, triggering adaptive immunity targeting the tumor [13-17]. Moreover, rapid CAR-mRNA constructs can replace CAR-DNA constructs based on nanobody- or/and bispecific antibodies-scFvs accelerating utility and effectiveness of CAR-T or CAR-NK strategy [8,18-20]. We have recently adopted this strategy to produce anti-PD-L1 Nbs in mice in a xenograft mouse CRC model. We found that LNP-encapsulated PD-L1Nb-mRNA significantly suppressed CRC progression (Chu et al. unpublished data).

Future Prospective

CRC tumorigenesis is a consequence of multi-faceted effects, and a single-agent therapy is unlikely to eliminate CRC tumors. Moreover, there is an unmet need for strategies that precisely deliver components of immunotherapy to the tumor site and modify the Tumor Microenvironment (TME) in cold CRC. These strategies are expected to enhance effectiveness and reduce adverse effects. Furthermore, integrated immunotherapeutic approaches utilizing mRNA platforms, nanobody/scFvs, synthetic Notch/specific receptors, probiotic-guided CAR-T/NK cells, immune checkpoint inhibitors, vaccines, and innate immune agonists will be more powerful and efficacious in the treatment of solid tumors, including CRC [12,13,17,19,21].

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