REVIEW ARTICLE

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Enhancing Anti-PD-1 Antibody Treatment in Colorectal Cancer: The Contribution of Innovative Immune Boosters and Inhibiting the USP2-PD-L1 Pathway

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Abstract

Background: Colorectal cancer (CRC) remains a major global health issue, with advanced stages difficult to treat. Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 pathway have improved cancer care, but they work well only in a small group of CRC patients with high microsatellite instability (MSI-H). Most CRC cases are microsatellite stable (MSS) and do not respond to ICI treatment alone, highlighting the need for combined therapies.

Methods: This review summarizes recent studies from PubMed, Google Scholar, and clinical trial databases up to 2025 focusing on why CRC resists ICI treatment. It examines ways to modify the immunosuppressive tumor microenvironment (TME), including using immune-boosting agents and targeting proteins like USP2 that regulate PD-L1.

Results: The immunosuppressive TME in MSS-CRC limits the effectiveness of PD-1 blockers. Immune adjuvants, such as the peptide NCL-P2, can reshape the TME by activating immune cells, increasing T cell entry into tumors, and reducing T cell exhaustion. Additionally, recent studies show that USP2 helps stabilize PD-L1 in cancer cells. Blocking USP2 leads to PD-L1 breakdown, improving T cell attack and boosting anti-PD-1 therapy in lab studies.

Conclusion: Combining anti-PD-1 antibodies with treatments that alter the immunosuppressive TME—such as immune adjuvants to strengthen immune responses and USP2 inhibitors to lower PD-L1 levels—offers a promising multi-target strategy. This method could help overcome treatment resistance and extend immunotherapy benefits to more CRC patients.

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Introduction

Colorectal cancer (CRC) is a major global health burden, ranking as the third most common cancer and the second leading cause of cancer-related mortality worldwide (1). In China, CRC incidence has increased significantly and is now the second most diagnosed malignancy (2, 3). While surgery can be curative for early-stage CRC, advanced or metastatic disease remains difficult to manage. Standard treatments such as chemotherapy and radiotherapy are often limited by toxicity, the development of drug resistance, and poor efficacy against disseminated tumors (4).

Cancer immunotherapy, particularly immune checkpoint inhibitors (ICIs), has transformed the treatment landscape for many solid tumors (5, 6). Anti-PD-1/PD-L1 antibodies function by blocking the interaction between PD-1 on T cells and PD-L1 on tumor cells, thereby reactivating the anti-tumor immune response (7, 8). However, these agents demonstrate significant efficacy primarily in the 4–5% of CRC patients whose tumors exhibit high microsatellite

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instability (MSI-H) or mismatch repair deficiency (dMMR), which are characterized by high tumor mutational burden and increased immunogenicity (9, 10).

The majority of CRC cases are microsatellite stable (MSS) and possess an immunologically "cold" tumor microenvironment (TME). This TME is characterized by poor T cell infiltration, an abundance of immunosuppressive cells, and the expression of alternative immune checkpoints, rendering MSS-CRC largely resistant to PD-1/PD-L1 blockade monotherapy (11, 12). Consequently, novel combinatorial strategies are urgently needed to convert these "cold" tumors into "hot," immune-active environments.

One promising approach involves the use of immune adjuvants to initiate and potentiate an anti-tumor immune response. These agents can stimulate the innate immune system, enhance antigen presentation, and activate cytotoxic T cells (13, 14). Simultaneously, emerging research indicates that PD-L1 expression is critically regulated at the post-translational level through mechanisms such as deubiquitination. The deubiquitinating enzyme USP2 has been identified as a key stabilizer of PD-L1 protein, facilitating tumor immune evasion (15). Targeting USP2 represents a potential strategy to reduce PD-L1 levels and sensitize tumors to anti-PD-1 therapy.

This review discusses the challenges of anti-PD-1 therapy in CRC and explores two key combinatorial strategies: the application of immune adjuvants such as NCL-P2, and the inhibition of the USP2-PD-L1 axis to overcome therapeutic resistance.

Methods

This narrative review collected English-language studies from PubMed, Google Scholar, and Web of Science up to 2025. Search terms included "colorectal cancer," "anti-PD-1," "immune checkpoint inhibitors," "resistance," "tumor microenvironment," "immune adjuvant," "antigen-presenting cells," "USP2," "PD-L1 regulation," "deubiquitination," and "combination immunotherapy." References from selected articles were also reviewed. The review focused on original research, meta-analyses, systematic reviews, and key clinical trials exploring ICI resistance and new combination treatments for CRC. The information was combined to give a broad view of how targeting USP2 and using immune adjuvants could improve anti-PD-1 therapy.

Results & Discussion

The Immune Environment of CRC and Challenges for Anti-PD-1 Therapy

The TME in CRC influences how well immunotherapy works. MSS-CRC usually has few killer T cells and many immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) (16, 17). These cells release substances that weaken T cell function. Cancer-associated fibroblasts (CAFs) also create physical barriers and secrete chemicals that keep T cells out of the tumor (18, 19). Together, these factors make PD-1 blockade alone ineffective in most MSS-CRC patients.

Immune Adjuvants to Boost ICI Effectiveness

Immune adjuvants aim to activate the innate immune system to support anti-tumor immunity. Toll-like receptor (TLR) agonists, such as CpG-ODN and Imiquimod, can activate dendritic cells and create a more inflammatory TME (20, 21). The peptide NCL-P2 has shown strong ability to activate multiple immune cells. In lab studies, NCL-P2 stimulates monocytes and dendritic cells to release inflammatory signals, promotes dendritic cell maturation, and enhances T cell activation (22). It can also enter cells directly, affecting internal signaling pathways (23). In mouse CRC models, combining NCL-P2 with anti-PD-1 antibodies reduced tumors more effectively and increased T cell entry into tumors compared to either treatment alone.

Targeting the USP2-PD-L1 Pathway to Reduce Immune Escape

Tumors use various methods to avoid immune detection. PD-L1 expression on tumor cells is regulated not only by gene activity but also by protein stability. Research shows that USP2 removes ubiquitin marks from PD-L1, preventing its degradation (15). Inhibiting USP2 reduces PD-L1 levels, improves T cell killing in lab tests, and enhances anti-PD-1 therapy in animal models. This also decreases immunosuppressive cells in the TME. These findings suggest USP2 is a valuable target to block a key immune escape route and improve ICI efficacy.

A Combined Approach: Boosting Immunity While Lowering PD-L1

Combining an immune adjuvant like NCL-P2 with a USP2 inhibitor and anti-PD-1 antibody offers a multi-action strategy. The adjuvant stimulates immune cells to launch an attack, while the USP2 inhibitor reduces the PD-L1 protection on tumor cells, making them more vulnerable. This dual approach—strengthening the immune response and weakening tumor defenses—could overcome resistance in MSS-CRC. Early data also suggests NCL-P2 might inhibit USP2 itself, adding another layer of synergy. Future studies should confirm this mechanism and test specific USP2 inhibitors with immune-stimulating treatments.

Conclusion

The poor response to anti-PD-1 therapy in MSS colorectal cancer shows the complexity of the tumor microenvironment and multiple resistance mechanisms. Combination therapies are necessary to break this resistance. This review emphasizes two promising strategies: using immune adjuvants like NCL-P2 to trigger an immune response and inhibiting USP2 to lower PD-L1 levels and disrupt immune evasion.Integrating these approaches could help extend immunotherapy benefits to more colorectal cancer patients.

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Authors Contributions

The authors contributed to the data analysis. Drafting, revising and approving the article, responsible for all aspects of this work.

Conflict of Interest

None

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