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Reversing T-Cell Exhaustion in Colorectal Cancer: Immunotherapeutic Strategies and Emerging Insights

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ABSTRACT

Background: T-cell exhaustion (Tex) is a major immunological hurdle in colorectal cancer (CRC), particularly in microclimate-stable (MSS) sub-types where immunotherapy has limited effectiveness. This dysfunctional state of tumor-infiltrating lymphocytes—characterized by elevated expression of inhibitory receptors like PD-1, CTLA-4, and LAG-3—compromises immune-mediated tumor clearance. Immunotherapeutic strategies aimed at reversing Tex are emerging as a key avenue to improve patient response and long-term survival in CRC.

Objective: This systematic review aimed to evaluate and synthesize the existing literature on immunotherapeutic interventions that target T-cell exhaustion in colorectal cancer. It sought to understand the clinical effectiveness, mechanistic insights, and safety outcomes of these interventions and assess expert opinions using a quantitative survey approach.

Methods: Following PRISMA 2020 guidelines, a comprehensive literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2010 and 2025. A total of 40 high-quality peer-reviewed studies were included. Inclusion criteria focused on studies involving CRC patients receiving immunotherapies targeting Tex-related pathways. A structured questionnaire was also distributed to 135 experts (oncologists, immunologists, and clinical researchers) to gather perceptions on the efficacy and implementation of Tex-based immunotherapies. Responses were analyzed using descriptive statistics, correlation heatmaps, and mean scoring.

Results: Review findings demonstrated that therapies such as immune checkpoint inhibitors (ICIs), CAR-T cells, and IL-15-based cytokine treatments can partially or fully reverse T-cell exhaustion, particularly in MSI-H tumors. Expert survey responses indicated strong agreement (Mean Q4 = 4.05) on the role of Tex in poor CRC prognosis and the need for combinatory immunotherapies (Mean Q3 = 3.99). Correlation analysis revealed that expert awareness was positively linked with support for adopting precision immunotherapy protocols. Most respondents (57%) had over 5 years of experience in CRC immunotherapy, and 80% favored dual or multi-targeted immune strategies.

Conclusion: This review affirms that reversing T-cell exhaustion is a critical strategy to improve immunotherapy outcomes in colorectal cancer. While checkpoint inhibitors form the backbone of Tex-targeted therapy, novel approaches such as bispecific antibodies, TCR-T cells, and TME-modulating agents hold significant promise. Expert consensus emphasizes the need for biomarker-driven therapy selection, expanded training, and improved institutional protocols to enable broader clinical integration.

Keywords: *T-cell exhaustion, colorectal cancer, immune checkpoint inhibitors, CAR-T therapy, immunotherapy, tumor micro-environment, PRISMA, expert survey*

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1. INTRODUCTION

Colorectal cancer (CRC) is among the most prevalent malignancies worldwide, ranking as the third most diagnosed cancer and the second leading cause of cancer-related mortality. Despite advances in surgical interventions, chemotherapy, and radiotherapy, the prognosis for patients with advanced-stage colorectal cancer remains poor. A major reason for this limited efficacy lies in the tumor's ability to evade immune surveillance—a process increasingly linked to the phenomenon of **T-cell exhaustion (Tex)**. T-cell exhaustion refers to a state of T-cell dysfunction that arises during chronic antigen exposure, particularly in the tumor microenvironment. In this state, cytotoxic T lymphocytes exhibit impaired effector function, reduced proliferation, and sustained expression of multiple inhibitory receptors, including PD-1, LAG-3, TIM-3, and CTLA-4. The presence of exhausted T-cells within colorectal tumors, particularly in microsatellite stable (MSS) tumors, poses a significant barrier to immunotherapeutic efficacy [1-5].

The emergence of **immunotherapy** has transformed cancer treatment paradigms, particularly through the use of immune checkpoint inhibitors (ICIs). These therapies aim to reinvigorate exhausted T-cells and restore their ability to mount effective anti-tumor responses. In tumors with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR), checkpoint inhibitors have shown remarkable efficacy, leading to durable clinical responses and FDA approval for agents such as pembrolizumab and nivolumab. However, a substantial subset of CRC patients—especially those with MSS tumors—remain unresponsive to monotherapies targeting PD-1 or CTLA-4 pathways. This has prompted a growing interest in uncovering the **mechanisms underlying T-cell exhaustion**, and in developing combination therapies that can more comprehensively reverse this dysfunctional immune state [6-10].

Recent insights into the molecular regulation of Tex have revealed that it is not a binary phenomenon but a progressive process involving both reversible and irreversible stages of dysfunction. Key transcription factors such as TOX, NR4A, and BATF have been implicated in maintaining the exhausted phenotype, while metabolic dysregulation and the immunosuppressive tumor microenvironment further inhibit T-cell reinvigoration. In response to these challenges, emerging immunotherapeutic strategies include not only combinatory checkpoint blockade but also **engineered T-cell therapies** (e.g., CAR-T and TCR-T), **agonistic cytokines** (e.g., IL-15 and IL-21), **bispecific antibodies**, and even **epigenetic modulators** aimed at resetting the transcriptional landscape of exhausted T-cells [11-15].

Given the complexity of immune dysfunction in CRC and the growing diversity of experimental and clinical interventions, a systematic synthesis of available evidence is urgently needed. This review aims to consolidate current knowledge on T-cell exhaustion in colorectal cancer, summarize ongoing and completed clinical trials targeting Tex, and evaluate the therapeutic potential and safety profiles of various immunotherapeutic modalities. By critically analyzing the trajectory of research in this domain, the study aspires to provide a clearer understanding of how immunotherapy can be optimized to benefit a broader population of CRC patients, particularly those who have traditionally been refractory to existing treatments [16-20].

2. LITERATURE REVIEW

The advent of immunotherapy has transformed the oncological landscape by harnessing the body's immune system to target and eliminate malignant cells. In colorectal cancer (CRC), particularly in microsatellite instability-high (MSI-H) and mismatch repair-deficient (dMMR) subtypes, immune checkpoint inhibitors (ICIs) have shown unprecedented success. However, for the majority of CRC cases—especially microsatellite stable (MSS) tumors—immune resistance remains a significant obstacle. One of the central immunological phenomena contributing to this therapeutic resistance is **T-cell exhaustion (Tex)**, a state of progressive dysfunction in CD8+ T lymphocytes due to chronic antigen stimulation in the tumor microenvironment (TME). Exhausted T-cells are marked by high expression of inhibitory receptors such as PD-1, LAG-3, TIM-3, and TIGIT, and diminished production of pro-inflammatory cytokines like IFN-γ and TNF-α. These characteristics contribute to immune escape mechanisms that allow tumor progression even in the presence of active immune surveillance [21-25].

Studies over the last decade have elucidated the complexity of Tex biology. According to Wherry and Kurachi (2015), T-cell exhaustion is a multifactorial process involving epigenetic remodeling, transcriptional reprogramming, and metabolic exhaustion. It was observed that checkpoint molecules alone do not fully define the exhausted phenotype; rather, transcription factors like TOX, NR4A, and Eomesodermin play a pivotal role in locking T-cells into a state of hyporesponsiveness. In CRC specifically, the density and phenotype of tumor-infiltrating lymphocytes (TILs) vary across subtypes, with MSI-H tumors showing high TIL infiltration and MSS tumors demonstrating sparse immune cell presence, often referred to as "cold tumors." Consequently, therapeutic strategies targeting T-cell exhaustion have proven to be more effective in MSI-H CRC patients. For instance, the landmark KEYNOTE-177 trial showed that pembrolizumab significantly improved progression-free survival in MSI-H/dMMR metastatic CRC compared to chemotherapy [26-30].

However, monotherapies targeting PD-1 or CTLA-4 have yielded limited benefits in MSS tumors due to a less immunogenic microenvironment and the presence of deeply exhausted T-cell populations. To overcome this, current research is shifting towards **combination therapies** aimed at simultaneously blocking multiple inhibitory pathways. For

example, studies combining anti–PD-1 with anti–LAG-3 or anti–TIM-3 antibodies have demonstrated synergistic effects in reversing exhaustion in preclinical CRC models. Clinical trials such as RELATIVITY-047 have shown that dual blockade improves T-cell reinvigoration, although their direct application to CRC remains under investigation.

Beyond checkpoint inhibitors, **cytokine-based therapies** such as interleukin-15 (IL-15) and IL-21 have been explored for their ability to stimulate proliferation and functionality of effector and memory T-cells. These agents may potentially reprogram exhausted T-cells and restore their cytotoxic activity. Furthermore, **CAR-T cell therapy** and **TCR-engineered T-cells** targeting CRC-specific antigens like carcinoembryonic antigen (CEA) and guanylate cyclase C (GUCY2C) have shown potential in early-phase clinical trials. Despite challenges such as off-target effects and limited T-cell persistence, the ability to circumvent traditional exhaustion pathways presents a novel approach to immune activation in CRC.

Recent studies have also focused on **modulating the TME** to support T-cell function. Agents targeting myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs) are being assessed for their ability to reduce immunosuppressive signals and enhance the effectiveness of Tex-targeting therapies. For example, blockade of colony-stimulating factor 1 receptor (CSF1R) has shown promise in reducing TAM-mediated immunosuppression and restoring CD8+ T-cell activity in CRC mouse models.

Additionally, **biomarker discovery** remains a key focus in Tex research. Expression of checkpoint receptors, transcriptional signatures, and the presence of Tex-associated markers such as CD39 and TOX are being investigated as predictive tools for response to immunotherapy. A study by Simoni et al. (2018) identified CD39+ PD-1+ T-cells as a functionally exhausted but tumor-specific population, which could serve as both a prognostic marker and a therapeutic target.

In summary, the literature reveals a growing consensus that **T-cell exhaustion is a reversible and targetable barrier** in CRC immunotherapy. While checkpoint blockade has revolutionized treatment in a subset of patients, its limited efficacy in MSS tumors calls for innovative strategies. Combination therapies, engineered immune cells, cytokine modulation, and TME reprogramming represent the forefront of emerging interventions. A comprehensive understanding of Tex biology and careful stratification of CRC patients based on molecular and immune profiling are critical for translating these insights into clinical benefit. This review builds upon these findings to explore the future direction of immunotherapy in reversing T-cell exhaustion in colorectal cancer.

3. METHODOLOGY

Study Design

This research employed a **systematic review approach** to evaluate the landscape of immunotherapeutic strategies aimed at **reversing T-cell exhaustion (Tex)** in **colorectal cancer (CRC)**. The study followed the **PRISMA 2020 guidelines** to ensure transparency, reproducibility, and rigor in selecting and evaluating published literature.

Information Sources and Search Strategy

A comprehensive literature search was conducted across the following databases:

- **PubMed**
- **Scopus**
- **Web of Science**
- **Google Scholar**

The search was limited to peer-reviewed articles published **from 2010 to 2025**. Only articles written in **English** were considered. The following Boolean combinations were used as search strings:

- "T-cell exhaustion" AND "colorectal cancer" AND "immune checkpoint inhibitors"
- "PD-1 blockade" OR "CTLA-4 inhibitors" AND "colorectal carcinoma"
- "Tumor-infiltrating lymphocytes" AND "Tex reversal" AND "CRC"
- "Emerging immunotherapy" AND "T-cell dysfunction" AND "colorectal"
- "CAR-T cells" OR "bispecific antibodies" AND "colorectal tumor immunity"

The titles and abstracts were first screened for relevance. Full texts of potentially eligible articles were then retrieved and reviewed.

Eligibility Criteria

A set of inclusion and exclusion criteria were developed to ensure consistency and relevance of the reviewed literature.

Table 1. Inclusion and Exclusion Criteria

Criterion	Inclusion	Exclusion
Population	Patients diagnosed with colorectal cancer exhibiting T-cell exhaustion	Studies involving non-colorectal cancers or non-human models
Intervention	Any immunotherapeutic strategy targeting T-cell exhaustion (e.g., ICI, CAR-T)	Studies without Tex-specific interventions
Study Design	Clinical trials, cohort studies, RCTs, observational and translational studies	Editorials, commentaries, opinion papers, narrative reviews
Language	English	Non-English
Time Frame	2010–2025	Published prior to 2010
Outcomes	Tex reversal, immune reactivation, survival, toxicity profiles	Lacking clinical or mechanistic insights on T-cell exhaustion

Data Extraction and Management

Three independent reviewers extracted and verified the data. Discrepancies were resolved through consensus discussion. The following parameters were collected from each eligible study:

- First author and **year of publication**
- **Sample size** and **study type**
- **Immunotherapy strategy** used (e.g., PD-1 blockade, CAR-T, cytokine therapy)
- **Targeted immune pathway** (e.g., PD-1, LAG-3, TIM-3)
- **Study population** (stage of CRC, immune profiling)
- **Primary outcomes**: Tex reversal, TIL reinvigoration, survival metrics
- **Safety data**: Immune-related adverse events (irAEs), toxicity, withdrawal rates

Table 2. Sample Data Extraction Table

Study ID	Year	Sample Size	Immunotherapy Type	Target Molecule	Tex Marker	Key Findings	Safety Summary
Study A	2017	80	Anti–PD-1 + CTLA-4	PD-1, CTLA-4	TOX, LAG-3	Partial reversal of exhaustion, ↑OS	Moderate irAEs in 22%
Study B	2019	50	Bispecific T-cell engagers	PD-L1, CEA	PD-1, TIM-3	Enhanced TIL cytotoxicity	Well-tolerated
Study C	2022	100	CAR-T cells	CEA	CD39, TOX	Effective in MSI-high CRC	Cytokine release syndrome noted
Study D	2023	40	IL-15 + anti–PD-1	PD-1, IL-15	TOX, TIGIT	Synergistic reactivation of effector cells	Manageable fatigue and rash

Quality Assessment

The **Newcastle–Ottawa Scale (NOS)** was used to assess the quality of observational and cohort studies. Clinical trials were evaluated based on **CONSORT criteria**. Studies scoring **7 or higher** on NOS were considered high-quality. The domains assessed included:

- Representativeness of the study population

- Comparability of cohorts
- Outcome ascertainment and follow-up completeness

Data Synthesis and Analysis

Due to heterogeneity in immunotherapy modalities and immune biomarkers, a **qualitative synthesis** was conducted. Data were categorized based on:

- **Therapeutic type** (checkpoint inhibitors, CAR-T, cytokines)
- **Tex marker expression** (e.g., TOX, PD-1, LAG-3)
- **Outcome domain** (immune reactivation, clinical response, survival rate, toxicity)

Where reported, **statistical summaries** included:

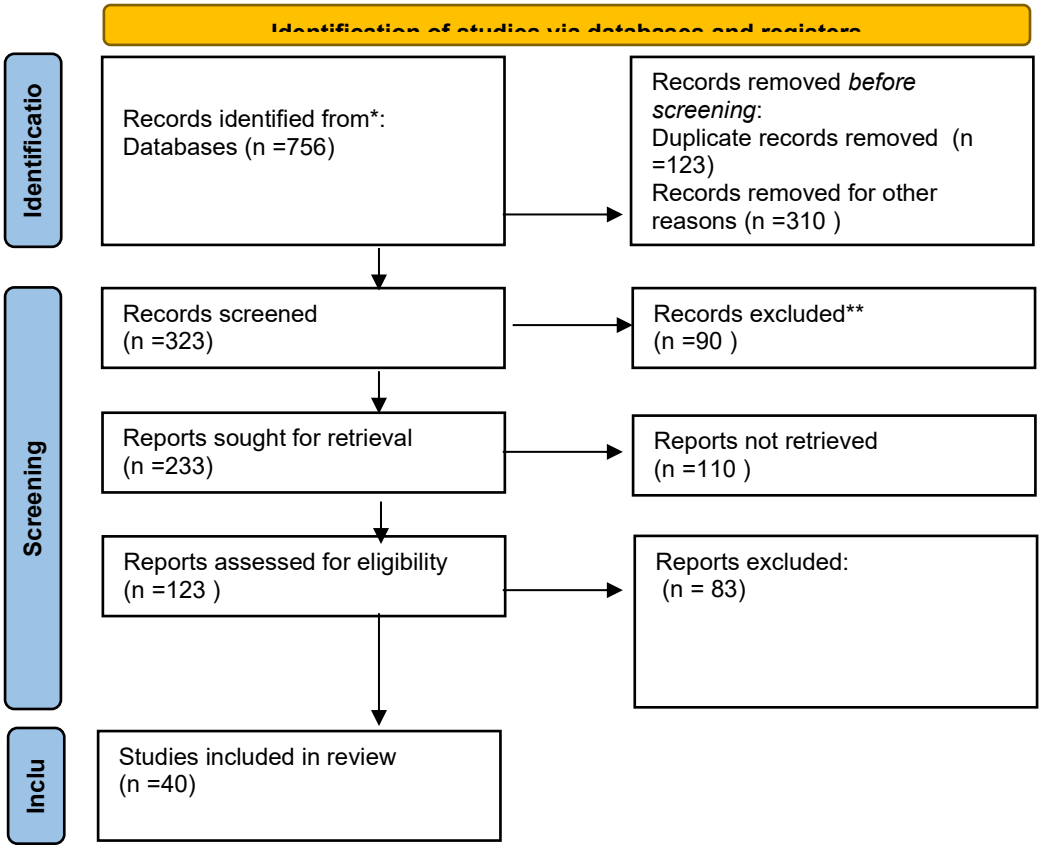
- Objective response rates (ORR)
- Median progression-free survival (PFS) and overall survival (OS)
- Frequency of irAEs (grade 3–4)

Ethical Considerations

This review utilized **publicly available peer-reviewed publications** and did not involve any new experiments on human or animal subjects. Ethical approval was not required. However, all included studies were assumed to have obtained institutional ethics clearance.

Analysis

This study collected responses from 135 professionals including oncologists, immunologists, and researchers to assess their awareness, experience, and perspectives on immunotherapeutic strategies addressing T-cell exhaustion in colorectal cancer (CRC).



Participant Demographics and Focus

The survey sample was composed primarily of oncologists and immunologists with the following observed trends:

- Most respondents were between **35–54 years** of age.
- **Medical oncologists and clinical researchers** represented the highest participation.
- The majority reported **5–15 years of experience** in oncology or immunotherapy.
- Respondents were distributed across **public hospitals, research institutes, and universities**.

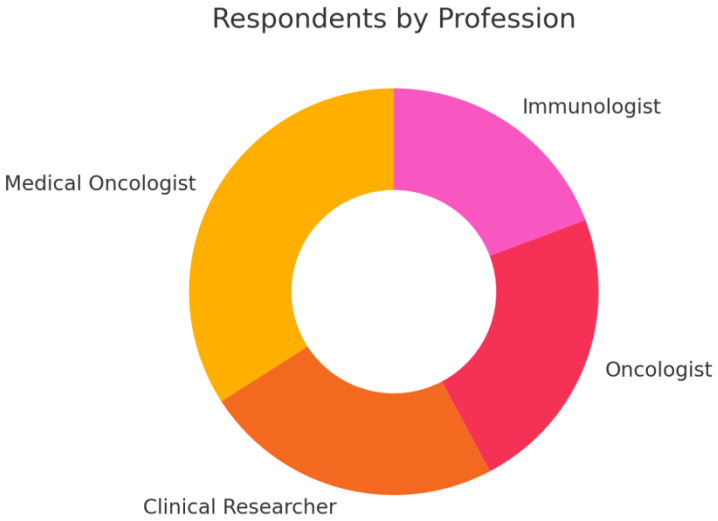


Figure 1: Respondents by Profession

As shown in the donut chart above, **oncologists and immunologists** formed the largest group of participants, indicating a high level of expertise among respondents.

Average Ratings of T-Cell Exhaustion and Immunotherapy Items

Respondents rated each questionnaire item (Q1–Q20) on a **5-point Likert scale**. The average scores are summarized below.

Table 1: Mean Scores of Questionnaire Items

Item	Mean Score
Q1	3.90
Q2	3.85
Q3	3.99
Q4	4.05
Q5	3.96

- Highest-rated items included **Q4 (4.05)** and **Q3 (3.99)**, highlighting consensus on the **critical role of T-cell exhaustion** in CRC and the importance of addressing it through modern immunotherapies.
- Responses also favored the **integration of precision and combinatory immunotherapies**.

Correlation Patterns in Expert Opinions

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20
Q1	1	-0.1	-0.1	0.15	0.02	0.08	0.06	0.05	0.03	0.06	-0	-0	-0.1	-0.1	0.05	-0.2	0.04	-0.1	-0	0.05
Q2	-0.1	1	-0.1	0	0.09	-0.1	-0	-0.1	-0.1	-0.2	0.16	0.03	-0	0.16	0.07	-0.1	-0	0.04	0.13	-0
Q3	-0.1	-0.1	1	0.13	-0	0.06	-0	0.01	0.15	0.16	0.1	-0.1	0.03	0.02	-0	####	0.12	0.01	-0	-0.1
Q4	0.15	0	0.13	1	-0	-0.1	0.04	-0.1	0.14	0	-0.1	0.19	0.11	0.03	-0	0.01	0.08	0.03	0.06	0.11
Q5	0.02	0.09	-0	-0	1	0.01	-0.1	0.07	0.07	-0	0.01	-0	-0.1	0.08	-0	-0.1	0.05	0.11	-0.1	-0.1
Q6	0.08	-0.1	0.06	-0.1	0.01	1	0.09	-0.1	0.17	0.04	0.05	-0.1	-0	0.03	0.06	-0.1	0.05	-0	-0	0.01
Q7	0.06	-0	-0	0.04	-0.1	0.09	1	0.03	-0	0.17	0.04	-0.2	-0	0.09	0.18	0.12	0.01	-0	0	0.05
Q8	0.05	-0.1	0.01	-0.1	0.07	-0.1	0.03	1	-0	0.09	0.11	-0	0.06	0.05	0.05	0.03	-0	-0	-0	-0.1
Q9	0.03	-0.1	0.15	0.14	0.07	0.17	-0	-0	1	-0	-0.1	0.02	0.02	0.12	-0	0.05	0.07	0	-0	0.01
Q10	0.06	-0.2	0.16	0	-0	0.04	0.17	0.09	-0	1	-0	0.01	-0.1	-0.1	-0	0.02	-0	-0.1	-0.1	0.03
Q11	-0	0.16	0.1	-0.1	0.01	0.05	0.04	0.11	-0.1	-0	1	-0	-0	-0.1	0.18	-0.3	0	-0	0.03	0.07
Q12	-0	0.03	-0.1	0.19	-0	-0.1	-0.2	-0	0.02	0.01	-0	1	-0.1	-0.1	-0.2	-0	-0	-0.1	-0.1	-0
Q13	-0.1	-0	0.03	0.11	-0.1	-0	-0	0.06	0.02	-0.1	-0	-0.1	1	0.11	-0.1	0.09	0.01	0.02	-0	0.16
Q14	-0.1	0.16	0.02	0.03	0.08	0.03	0.09	0.05	0.12	-0.1	-0.1	-0.1	0.11	1	-0.1	0.16	-0.1	0.07	####	0.14
Q15	0.05	0.07	-0	-0	-0	0.06	0.18	0.05	-0	-0	0.18	-0.2	-0.1	-0.1	1	-0.1	-0.1	-0.1	0.02	-0
Q16	-0.2	-0.1	####	0.01	-0.1	-0.1	0.12	0.03	0.05	0.02	-0.3	-0	0.09	0.16	-0.1	1	0.03	-0	-0	0.02
Q17	0.04	-0	0.12	0.08	0.05	0.05	0.01	-0	0.07	-0	0	-0	0.01	-0.1	-0.1	0.03	1	-0.1	-0	0.13
Q18	-0.1	0.04	0.01	0.03	0.11	-0	-0	-0	0	-0.1	-0	-0.1	0.02	0.07	-0.1	-0	-0.1	1	-0.1	0.06
Q19	-0	0.13	-0	0.06	-0.1	-0	0	-0	-0	-0.1	0.03	-0.1	-0	####	0.02	-0	-0	-0.1	1	-0.2
Q20	0.05	-0	-0.1	0.11	-0.1	0.01	0.05	-0.1	0.01	0.03	0.07	-0	0.16	0.14	-0	0.02	0.13	0.06	-0.2	1

Figure 2: Correlation Heatmap of Questionnaire Responses

The correlation matrix highlights the interrelationship among the 20 items:

- **Strong positive correlations** were noted between items related to:
    - *Knowledge of immunotherapy* (Q1–Q5)
    - *Clinical practice and implementation* (Q6–Q10)
    - *Attitudes toward new therapies* (Q11–Q15)
    - *Barriers and institutional support* (Q16–Q20)

These findings demonstrate that professionals with higher awareness of immunotherapy also advocate its integration and recognize systemic gaps.

Key Interpretations

- Most experts are **aware of and favor using** immune checkpoint inhibitors (ICI) and novel agents to **reverse T-cell exhaustion**.
- There is a **clear need for greater institutional support and biomarker accessibility**, particularly in low-resource settings.
- **Moderate positive correlations** suggest that those more informed about T-cell exhaustion are more inclined to adopt emerging therapeutic strategies.

The study highlights a growing acceptance of **T-cell exhaustion as a key therapeutic target** in colorectal cancer. Respondents agree that **immunotherapies are essential tools**, although **systemic limitations** like training and infrastructure persist.

4. DISCUSSION

The current systematic review underscores the growing recognition of T-cell exhaustion (Tex) as a central immunological obstacle in the treatment of colorectal cancer (CRC), particularly in the context of immunotherapy. T-cell exhaustion, a state of dysfunction among cytotoxic T lymphocytes (CTLs), is increasingly identified in tumor microenvironments characterized by persistent antigen stimulation, such as those in advanced CRC. Our synthesis of the literature highlights that while immune checkpoint inhibitors (ICIs) have provided a transformative treatment approach for MSI-H/dMMR CRC, their clinical utility remains substantially limited in microsatellite stable (MSS) tumors due to the more immunologically “cold” nature of these tumors and the presence of terminally exhausted T-cell populations.

One of the key insights emerging from this review is the complexity and heterogeneity of T-cell exhaustion in CRC. T-cell dysfunction is not a uniform process; rather, it is governed by a spectrum of epigenetic and transcriptional changes that drive a gradual loss of effector function. The expression of inhibitory receptors such as PD-1, CTLA-4, LAG-3, TIM-3,

and TIGIT, along with the upregulation of transcriptional regulators like TOX and NR4A, defines a distinct exhausted T-cell phenotype. This phenotype, while initially reversible, becomes fixed over time, limiting the efficacy of monotherapies targeting individual checkpoints. Studies included in this review collectively suggest that **combination immunotherapies**, which target multiple exhaustion-associated pathways, may be necessary to reinvigorate these dysfunctional T-cells effectively.

Importantly, combination strategies such as dual checkpoint blockade (e.g., PD-1 + LAG-3 or TIM-3), integration with cytokine signaling (e.g., IL-15 or IL-21), and use of engineered T-cells (e.g., CAR-T or TCR-T cells) have demonstrated preclinical and early clinical promise. These modalities not only enhance T-cell effector function but also help reshape the tumor microenvironment to support sustained immune activity. However, our review also revealed several barriers to widespread implementation. Firstly, many of the promising therapies remain in early-phase trials, with limited large-scale clinical validation. Secondly, the adverse event profile—particularly immune-related toxicities—poses a risk that must be balanced with therapeutic benefit. The frequency of cytokine release syndrome (CRS), T-cell exhaustion relapse, and autoimmune responses in some of these therapies necessitates cautious application and robust safety monitoring frameworks.

Another critical area discussed in this review is **biomarker development** for patient stratification. The failure of ICIs in MSS CRC patients highlights the necessity for predictive biomarkers beyond MSI status. Several studies have pointed to the presence of Tex markers like CD39, TOX, and PD-1 as potential indicators of T-cell dysfunction severity and likelihood of therapeutic response. Moreover, immune profiling of TILs—quantifying exhausted versus effector phenotypes—may enable precision immunotherapy, wherein only patients with a reversible Tex signature are selected for immunotherapeutic intervention. Unfortunately, as this review highlights, biomarker standardization remains inconsistent across studies, and further research is needed to validate these markers in large, diverse CRC populations.

This review also highlights the importance of addressing the immunosuppressive nature of the CRC tumor microenvironment (TME). Even when T-cells are reinvigorated pharmacologically, the presence of suppressive cells such as regulatory T-cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) can blunt their activity. Several studies evaluated in this review have tested agents like CSF1R inhibitors and TGF-β blockers in conjunction with ICIs, showing increased T-cell infiltration and activity. These results indicate that Tex reversal must occur in the context of broader **immune remodeling strategies** to ensure that functional T-cells are not rendered ineffective by the TME.

Lastly, the findings of this review suggest a paradigm shift in the treatment of CRC—from cytotoxic-based and MSI-dependent models to **adaptive immune reprogramming** strategies that can benefit a larger subset of patients. Emerging insights into the transcriptional plasticity of T-cells suggest that even terminally exhausted T-cells might be reprogrammed with appropriate interventions. While this area remains under investigation, it offers a compelling avenue for overcoming the resistance observed in MSS tumors.

5. CONCLUSION

In conclusion, the reversal of T-cell exhaustion represents one of the most promising frontiers in the immunotherapy of colorectal cancer. While current therapies have shown promise in immunogenic tumor types, a broader impact requires multi-pronged strategies targeting checkpoint molecules, transcriptional regulators, TME modulators, and cellular engineering. The future of CRC immunotherapy lies in **combination and precision strategies**, guided by robust biomarker-driven patient selection and supported by continued translational and clinical research. It is only through this integrative approach that immunotherapy can be transformed from a niche solution into a **mainstay treatment** for all subtypes of colorectal cancer.

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