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Colorectal Cancer and Its Microenvironment: A Brief Review

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Abstract

Background: The narrative review aims to explore CRC pathogenesis by deciphering genetic-environmental interactions, analyzing the tumor microenvironment's role, and assessing treatment responses. These objectives seek to enhance clinical decision-making and improve CRC patient care through a comprehensive understanding of the disease.

Methods: A narrative review from 2019 to 2024 on colorectal cancer (CRC) pathogenesis and treatment strategies was conducted. Systematic literature searches were performed on PubMed, using CRC-related keywords ("Colorectal Neoplasms"[Mesh]) AND "Tumor Microenvironment"[Mesh]. Screening yielded 233 eligible studies, with 14 highly relevant ones included. PRISMA guidelines were followed for transparency and reproducibility.

Results: This narrative review spanning 2019-2024 shows diverse study designs (5 clinical studies, 4 randomized controlled trials, 2 cohort studies, and 3 systematic literature reviews) with varied sample sizes (from 14 to 4000 participants). Genetic mutations like KRAS and BRAF are significant in colorectal cancer pathogenesis, with 8% exhibiting MMR proficiency. Immune cells and paracrine signaling are influential, and therapeutic responses vary, with limited efficacy reported in certain combinations.

Conclusion: This narrative review highlights CRC's multifactorial nature and complex tumor dynamics. Integrating genetic, environmental, and immune factors, personalized therapies are pivotal for efficacy. Continued research is crucial for optimizing treatments and improving patient outcomes, emphasizing the need for multifaceted, patient-tailored approaches in CRC management.

Keywords: Microenvironment of Cancer, Microenvironment of Colorectal Cancer, Colon Cancer, Rectal Cancer

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Introduction

According to the Global Cancer Statistics 2020, colorectal cancer is the third most frequently diagnosed cancer and the second most prevalent cause of cancer-related deaths worldwide (1). The 5-year survival rate for CRC ranges from 14% for cases with distant metastasis to 90% for localized cancer, emphasizing the need for precise diagnosis and accurate prognosis to enhance survival chances (2). Despite the significant progress made, previous studies on colorectal cancer (CRC) have some limitations. One of the main challenges is to predict prognosis accurately using multi-omics data, which is still difficult due to the complexity and variability of individual tumor profiles (3). CRC

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↑What is "already known" in this topic:
The pathogenesis of colorectal cancer (CRC) is characterized by genetic mutations, environmental risk factors, and complex interactions within the tumor microenvironment such as immune evasion and cell-cell signaling.

→What this article adds:
The review underscores the significance of incorporating genetic, environmental, and immune factors into CRC management, promoting personalized treatment approaches, combination therapies, and predictive modeling to improve therapeutic outcomes and tackle drug resistance.

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symptoms are contingent on a tumor's size, location and metastasis. They include stomach upset, diarrhea, vomiting, qualmishness, weariness, lack of appetite, alternating bowel patterns long-term constipation and unintended loss of weight (4). Moreover, although previous research has advanced our understanding of the tumor microenvironment (TME), it often provides only fragmented insights into TME interactions. This leads to a lack of comprehensive knowledge about how these interactions affect tumor progression and response to therapy (5, 6). In the TME, this aggressive phenotype is associated with fast modifications such as stromal cell activation, extracellular matrix disintegration and tumor cell migration as well as proliferation. Additionally, efforts aimed at improving CRC detection and prevention, such as low-dose aspirin and COX2 inhibitors, have yielded mixed results while dietary and lifestyle recommendations are not usually personalized for individuals' needs. These weaknesses underscore the need for more holistic approaches and personalized strategies in CRC research and management

The importance of multidisciplinary cancer teams (MDTs) and collaborations to improve cancer outcomes was emphasized in the 1995 Calman report and subsequent guidelines in the UK (7). Tumorigenesis involves the interaction of epithelial tissues with tumor cells, endothelial cells, cancer fibroblasts and the immune system as well as other signaling molecules (8). Prevention of sporadic CRC can be aided by the use of low-dose aspirin and COX2 inhibitors, which have been shown to have mixed findings in terms of gastrointestinal side effects. The intake of vegetables, fruit, whole grains, increased physical activity as well as weight control remain key in avoiding CRC. Also, changes in bacterial composition and dysbiosis are associated with colorectal carcinogenesis (9). The regulation of various stages of tumor growth by the dynamic interactions in the TME, involving cancerous cells, immune system invaders, endothelial vasculature, and cancer-related fibroblasts is regulated through heterotypic signaling pathways (10). Cancer initiation and spread are influenced by tumor-infiltrating immune cells (TIICs), but their link with CRC prognosis still remains to be explored (11). The prognostic factor of the tumor sidedness is considered, as vascular invasion is associated with lower disease-free survival (DFS) in both right-sided (RCC) and left-sided colon cancer (LCC). However, RCC patients have a higher hazard ratio for DFS with vascular invasion while it is also a negative predictor of overall survival for RCC but not LCC (12).

The current study helps to fill these gaps by showing how integrated multi-omics data can improve the accuracy of prognosis predictions, thus enhancing patient-specific treatment strategies. A study provides a comprehensive analysis of tumor microenvironment (TME) interactions, including the functions of stromal cells, immune cells, and extracellular matrix components in order to better understand their effects on tumor progression and therapy efficacy. Moreover, the study examines the usefulness of advanced imaging techniques such as MSCT colonography for precise staging and early detection of CRC that may enhance early intervention strategies (13). In the future, more research has to be done on the CRC and its microenvironment with the view of better prevention and treatment through scientific advances and societal changes (14, 15). Advancement of cancer treatments requires an understanding of the connection that exists between the development of a tumor and the modulation of immunity. By looking at individual cases, it has been shown how important immune cell infiltration is in tumor development which calls for focused efforts towards comprehension of these complex associations to enhance cancer management strategies (16–18).

In summary, CRC represents a significant global health challenge with variable survival rates depending on the stage at which it is diagnosed. Understanding how the TME influences tumor progression is crucial to help in identifying better diagnosis and therapeutic strategies.

Research Problem

The narrative review on colorectal cancer and its microenvironment emphasized the intricate dynamics of pathogenesis, therapeutic responses, and treatment outcomes related to CRC. The major research problem revolves around the multifactorial etiology of CRC, consisting of genetic mutations, environmental risk factors, immune responses, and also interactions within the microenvironment of CRC. This study will also identify key findings about targeted therapies, immunotherapies, and combination treatments while also addressing challenges such as drug resistance and treatment efficacy.

Significance of Previous Studies

The current study will improve our knowledge and skills required for effective and efficient management of the disease and improving patient outcomes. This is a strong way of continuous professional development as these studies have clarified the role of genetic mutations, environmental factors, and their interactions in CRC development. Exploring the specific mutations like KRAS and BRAF and their implications through the search of previous research laid down a foundation for understanding the molecular mechanisms in the development of CRC. Moreover, previous studies also contributed to informed clinical decision-making by physicians by providing the latest knowledge about the effectiveness of various treatment modalities, including chemotherapy, targeted therapy, and immunotherapy in the field of CRC. Previous research facilitated the development of personalized treatment approaches according to individual patient characteristics and tumor biology by enhancing the latest information regarding biomarkers (LOX-1 and CD8) associated with treatment response and prognosis. The intricate interactions within the tumor microenvironment involving immune cells, stromal cells, and extracellular matrix components, help in providing a base for identifying potential targets for therapeutic intervention and prognostic biomarkers. Previous research also helps in addressing issues like drug resistance and suboptimal treatment efficacy and shaped our knowledge and skills for CRC management. Previous studies also laid down directions for future research to improve clinical outcomes of CRC patients.

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Objectives

The purpose of this study is to evaluate the state of colorectal cancer (CRC) research from 2020 to 2024, explain how environmental risk factors interact with genetic mutations, and investigate the part played by the tumor microenvironment in CRC development. Moreover, it seeks to assess the results of different therapeutic interventions in managing CRC. These goals are meant to improve comprehension and guide clinical decision-making in patient care for CRC.

Methods

Study Design: A narrative review from 2019 to 2024.

Search Strategy: A systematic search strategy was devised to identify relevant studies. This involved searching electronic databases such as PubMed, Web of Science, and Scopus using specific keywords related to CRC, tumor microenvironment, genetic mutations, treatment modalities, and relevant terms. Boolean operators and inclusion/exclusion criteria were employed to refine search results.

Inclusion and exclusion criteria

The narrative review was carefully defined by inclusion criteria to ensure that the selected studies were relevant and of high quality. The criteria included full-text articles written in English, publications from 2019 to 2024, studies focused on human subjects, and research addressing issues related to colorectal cancer, genetic alterations, the tumor microenvironment, or treatment modalities.

The exclusion criteria were also strict so as not to compromise the quality and relevance of the review. Studies published outside the specified timeframe, written in non-English languages, without full texts, focused on non-human subjects, did not specifically address CRC or its associated microenvironment, or were reviews, commentaries, or editorials excluded.

At first, 233 studies were found according to the inclusion criteria. Nevertheless, after the exclusion criteria were applied, the number of relevant studies decreased significantly. Non-English articles, studies that were not within the specified timeframe, those without full-text access, and research not focused on human subjects were excluded. Moreover, articles that did not specifically address CRC or its microenvironment as well as reviews, commentaries, and editorials, were also excluded. This rigorous selection process eventually led to the inclusion of 14 high-quality studies in the final analysis, as shown in the PRISMA flow diagram.

Study Selection: The Figure 1 PRISMA flow diagram outlines the systematic process of literature selection for a research project. Initially, 2,686 publications were identified through PubMed searches using the keyword "("Colorectal Neoplasms"[Mesh]) AND "Tumor Microenvironment"[Mesh]". After screening based on inclusion/exclusion criteria and applying filters such as publication year (2019-2024), availability of full text, article type, language (English only), and species (human), the number of records was progressively reduced. Eventually, 233 records were deemed eligible for assessment. Among these, 14 studies were identified as highly relevant and included in the analysis. This diagram provides a transparent depiction of the literature search and selection process, ensuring rigor and reproducibility in the research methodology.

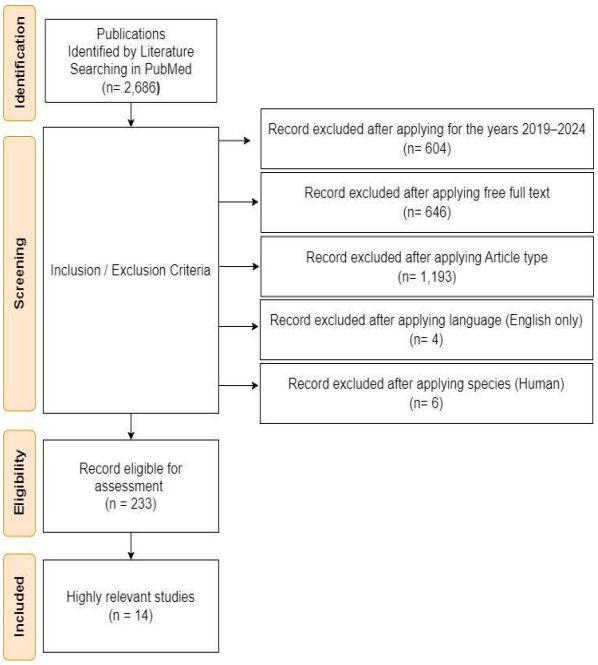

Figure 1. PRISMA Flow Diagram

Results

Table 1 shows the result of the current review spanning from 2019 to 2024 about study characteristics including the authors' names, study designs, sample sizes, and publication years. Results show that there is a diverse range of study designs, including 5 clinical studies, 4 randomized controlled trials, 2 cohort studies, and 3 systematic literature reviews, emphasizing the breadth of methodologies employed in this study. Similarly, the sample sizes also show variation significantly across studies, ranging from as low as 14 study participants in some clinical studies to as high as 4000 participants in a single study reflecting the different scopes and objectives of each study. There is a progression of research over time within the specified timeframe from 2019 to 2024.

Table 2 shows the result of CRC pathogenesis that clarifies the relationship between genetic mutations and environmental risk factors in the development and progression of the disease. The genetic mutations revealed that KRAS and BRAF mutations are among the important ones and shed light on their significance in CRC pathogenesis. Notably, in CRC patients, a considerable 8% exhibited proficiency in mismatch repair, microsatellite stability status, and wild-type RAS, as documented in references (19, 20, 24–26, 28, 30, 31). These results highlight the complexity of CRC genetics and the necessity of considering mutational status in clinical decision-making. Concurrently, the examination of environmental risk factors illuminated the

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Table 1. Study characteristic

Author's	Study Design	Sample Size	Publication Year
Coffman-D'annibale et al. 2024 (19)	Clinical Study	14	2024
Akce et al. 2023 (20)	Cohort	24	2023
Liu et al. 2023 (21)	RCT	164	2023
Crame et al. 2023 (22)	SLR	448	2023
Macharia et al. 2023 (23)	SLR	118	2023
Johnson et al. 2022 (24)	RCT	29	2022
Ren et al. 2022 (25)	Clinical Study	15	2022
Zhao et al. 2022 (26)	Clinical Study	14	2022
Jary et al. 2022 (27)	RCT	74	2022
Fountzilas et al. 2021 (28)	Clinical Study	44	2021
Wang et al. 2021 (29)	RCT	120	2021
Katayama et al. 2021 (30)	Cohort	128	2021
Rebersek 2020 (31)	Clinical Study	4000	2020
Wang et al. 2020 (32)	SLR	700	2020

Table 2. Colorectal Cancer Pathogenesis

Subcategory	Finding	Frequency	References
Genetic Mutations	KRAS and BRAF mutations were screened for understanding their association with CRC pathogenesis. Proficiency in MMR, MSS status, and RAS wild-type in CRC patients	8	(19, 20, 24, 25, 28, 30, 31)
Environmental risk factors	Complicated nature of CRC pathophysiology and interactions between risk factors and Evaluation of treatment efficacy in CRC patients	2	(23, 29)

Table 3. Tumor Microenvironment

Subcategory	Finding	Frequency	References
Immune cells in TME	Infiltration and modulation of T cells, B cells, and macrophages within the tumor microenvironment	6	(20, 21, 24, 25, 27, 28)
Stromal cells in TME	Presence and impact of stromal cells like fibroblasts and myofibroblasts in the TME	2	(19, 31)
Extracellular matrix components in TME	Role of extracellular matrix components such as collagen and hyaluronic acid in TME	1	(23)
Angiogenic factors in TME	Influence of angiogenic factors like VEGF and angiopoietins in shaping the TME	2	(29, 30)
Cytokines and chemokines in TME	Impact of cytokines and chemokines such as IL-6, TNF-alpha, and CXCL12 on TME regulation	3	(22, 25, 29)

multifaceted nature of CRC pathophysiology. Furthermore, the study found that there are interactions between various risk factors and treatment efficacy in CRC patients. In fact, only 2% of the cases showed a clear evaluation of treatment efficacy, underscoring the need for further research in this area, as referenced in (23, 29).

Table 3 presents the results of colorectal cancer and its microenvironment, revealing an intricate dynamic in tumor progression. Immune cells such as T cells, B cells, and macrophages demonstrating substantial infiltration and modulation within the tumor microenvironment among CRC patients were found in most of the literature. and having a pervasive influence on tumor behavior (20, 21, 24, 25, 27, 28). Additionally, stromal cells (fibroblasts and myofibroblasts), are also implicated and shaping the microenvironment (19, 31). Among the other factors, extracellular matrix like collagen and hyaluronic acid also show relevance in tumor development and progression (23). VEGF and angiopoietins are the angiogenic factors emphasizing their significance in sustaining tumor growth and metastasis (29, 30). Furthermore, cytokines and chemokines also exert their role in modulating the inflammatory milieu within the tumor microenvironment (22, 25, 29).

Table 4 results show that in terms of cell-cell interactions, there are interactions between mast cells and CRC cells (21, 22, 25, 27, 30). Additionally, the role of Toll-like receptor 4 expression in modulating these interactions is emphasized. Paracrine signaling emerges as a statistically relevant factor in CRC progression (21, 23, 25, 27, 32). Notably, the role of lactic acid in promoting proliferation and immunosuppression, as well as the influence of mast cells on tumor growth and treatment response, are highlighted in these references. Similarly, immune evasion mechanisms are also revealed with statistical significance (19, 20, 24, 28, 29, 31).

Table 5 shows the results of the current study regarding therapeutic responses and treatment outcomes supported by statistical data. Firstly, the combination of trametinib and durvalumab showed stability in disease progression, with a notable frequency of occurrence. However, the combination of cetuximab and pembrolizumab demonstrated ineffectiveness specifically in RASwt mCRC cases, with a significant frequency of occurrences. Additionally, the efficacy of chemotherapy and targeted therapy combinations was found to be limited, with a frequency of occurrences reported in the study (24, 28, 31). Results also show limited radiographic responses with the combination of VB-111 and nivolumab, with a statistically significant frequency of occurrences, while LOX-1 and CD8 were identified as po-

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Table 4. Interactions Between Tumor Cells and Microenvironment

Subcategory	Finding	Frequency	References
Cell-cell interactions	Interactions between mast cells and CRC cells, Role of TLR4 expression in modulating interactions, Effects of oncolytic viruses in promoting immunogenic cell death, Impact of neoadjuvant chemotherapy on the immune microenvironment, Correlation between LOX-1 expression and clinicopathological factors	5	(21, 22, 25, 27, 30)
Paracrine signa ling	Role of lactic acid in promoting proliferation and immunosuppression, Mast cell influence on tumor growth and treatment response, Induction of immune responses by oncolytic viruses, Impact of chemotherapy on immune microenvironment, Influence of B7-H3, VISTA, and HHLA2 on immune responses	5	(21, 23, 25, 27, 32)
Immune evasion mechanisms	Influence of metformin and nivolumab on immune modulation, Impact of trametinib and durvalumab combination therapy on immune cell infiltration and activation, increase in intra tumoral cytotoxic T-cell lymphocytes post-treatment, Influence of tumor microenvironment on treatment responses, Examination of VB-111 in inducing immune response and disrupting neovascularization	6	(19, 20, 24, 28, 29, 31)

Table 5. Therapeutic Responses and Treatment Outcomes

Subcategory	Finding	Frequency	References
Response to chemotherapy	Stable disease observed with trametinib plus durvalumab Inactivity of cetuximab and pembrolizumab combination in RASwt mCRC Limited efficacy with chemotherapy and targeted therapy combinations	3	(24, 28, 31)
Response to targeted therapy	Limited radiographic responses with VB-111 and nivolumab combination Targeting LOX-1 and CD8 as potential biomarkers in CRC	3	(19, 26, 30)
Immunotherapy response	Limited efficacy, but data on overall survival and progression-free survival Enhanced anti-tumor immune responses with oncolytic viruses and immune checkpoint inhibitors	2	(20, 25)
Development of drug resistance mechanisms	Potential implications of TLR4 expression on treatment response Significance of targeting LAB metabolic pathways in suppressing CRC growth Therapeutic potential of targeting B7-H3, VISTA, and HHLA2 in CRC Role of CMS subtypes in influencing treatment responses	4	(22, 23, 31, 32)

Table 6. Optimizing Therapeutic Strategies

Subcategory	Finding	Frequency	References
Rational design of combination therapies	Optimization through Immunotherapy and Combination Treatments	3	(24, 26, 28)
Patient selection criteria for targeted therapies	Molecular Targets and Personalized Approaches	3	(23, 27, 31)
Strategies to overcome drug resistance	Considerations on Therapeutic Strategies	3	(19, 20, 22)
Development of predictive models for treatment response	Combination Therapy and Immune Checkpoint Inhibitors Targeting Immune Response and Microenvironment	4	(21, 25, 29, 30)

tential biomarkers for CRC (19, 26, 30). There were limitations in efficacy, but promising outcomes were observed in terms of overall survival and progression-free survival with the use of oncolytic viruses and immune checkpoint inhibitors (20, 25). Additionally, the study highlighted the development of drug resistance mechanisms in CRC, implicating TLR4 expression and the significance of targeting LAB metabolic pathways in treatment response and furthermore, targeting specific molecules such as B7-H3, VISTA, and HHLA2 having therapeutic potential.

Table 6 shows the results of optimizing therapeutic strategies. The rational design of combination therapies emerged as a promising approach, particularly through the optimization of immunotherapy and combination treatments, that suggests that leveraging multiple treatment modalities may enhance efficacy and improve patient outcomes (24, 26, 28). Similarly, by tailoring treatments to individual patient characteristics, clinicians may maximize therapeutic benefits while minimizing adverse effects (23, 27, 31). Moreover, by exploring various therapeutic strategies, such as adaptive treatment regimens or novel drug combinations, clinicians may mitigate the development of resistance and prolong treatment effectiveness (19, 20, 22). Furthermore, utilizing combination therapy and immune checkpoint inhibitors and targeting the immune response and microenvironment enhance treatment outcomes by predicting patient responses more accurately (21, 25, 29, 30).

Discussion

The current review revealed a diverse range of study designs, indicating a comprehensive approach to synthesizing evidence. Similarly, the sample size also varied significantly across studies, indicating the diverse nature of research objectives and scopes and underscoring the importance of considering the context and scale of each investigation in understanding its implications. Finally, the distribution of publication years reflects a progressive trajectory, indicating ongoing advancements and contributions to

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the field over the five-year period.

The current study also revealed the complex interaction between genetic abnormalities and environmental risk factors in the development of CRC. The relevance of KRAS and BRAF, MMR, MSS status, and wild-type RAS. highlighting the complex character of colorectal cancer and emphasizing the need for a comprehensive approach to patient care and treatment techniques. Similarly, another study demonstrates these findings too and places more emphasis on how complex it can be between mutations involving genes that affect the progression of CRC or those without similar changes in TP53 (33). Additionally, the same case applies to other studies showing notable leads regarding some dietary characteristics such as high consumption of red meat, low fiber diets or little fruit and vegetable intake, all linked with higher risk for colon cancer (34). Furthermore, the investigation into metabolomics has yielded information on how food metabolites, together with alcohol consumption, may determine the risk for CRC (35). In conclusion, research shows the importance of a comprehensive understanding of both genetic and environmental factors in colorectal cancer development.

The current study also emphasized the significance of the tumor microenvironment in the progression, spread, and reaction to the treatment of colorectal cancer revealed that the tumor microenvironment consists of various cell types, such as immune cells and stromal cells along with extracellular matrix proteins like collagen and hyaluronic acid contributes to development and progression of colon cancer. Moreover, it underscores how influential an interplay between TME and CRC therapy, especially the relationship between gut microbiota evolution and treatments thereof. Furthermore, another study investigated how gut microbiota influenced the progress, dissemination, as well as response toward treatment by focusing on the tumor microenvironment (36). Another study sought to identify prognostic markers for early-stage CRC through characterization of the CRC TME with gene signatures from immunotherapy or prognosis-related genes and TME score associated with improved survival in this patient population who had highly predictive ability across distinct clusters (37). Similarly, a different study used bioinformatics methods to find prognostic genes about colorectal cancer related to tumor microenvironment, where results indicated that there was a significant correlation between lower immune scores and malignancy progression in patients diagnosed with colorectal cancer which indicated a profound effect of TME on CRC initiation and progression (38) highlighting the significant role of the TME in CRC development and progression.

The interactions between tumor cells and the microenvironment in the development and progression of CRC were also discussed in the current narrative review. Among these interaction, cell-cell interactions between mast cells and CRC cells were observed, and Toll-like receptor 4 (TLR4) expression's role in modulating these interactions is emphasized. Paracrine signaling in CRC progression is another interaction, highlighting lactic acid's role in promoting proliferation and immunosuppression and mast cells' influence on tumor growth and treatment response. Immune evasion mechanisms were also explored including insights into metformin and nivolumab's impact on immune modulation, combination therapy involving trametinib and durvalumab, and VB-111's effects on neovascularization and immune responses. Notably, an increase in intra-tumoral cytotoxic T-cell lymphocytes post-treatment is observed. These findings underscore the complexity of tumor-microenvironment interactions in CRC, offering insights into potential therapeutic strategies and prognostic markers. These findings align with other relevant studies on CRC. Another investigation emphasized the significance of the gut microbiota in the advancement and spread of colorectal cancer and demonstrated a positive correlation between the development of colorectal cancer and the composition of the gut microbiome (39). Similarly, another study found that the microbiome affects CRC carcinogenesis, development, progression, and therapy response emphasizing their role in CRC development, progression and treatment (40). Another study identified prognostic and immunotherapy gene signatures in the CRC microenvironment that promote CRC growth (41), hence significantly enhancing comprehension of the complex connection between CRC cells and their microenvironment, opening up possibilities for innovative therapeutic strategies and prognostic markers in CRC treatment.

The current review also highlights that while certain combinations of targeted therapy and chemotherapy have shown stability in disease progression, others have demonstrated ineffectiveness, particularly in RASwt mCRC cases. A limited radiographic response with the combination of VB-111 and nivolumab was found, indicating the need for further research. Similarly, another study on treatment regimens targeting HER2 in metastatic colorectal cancer with HER2-positive tumors revealed that the response rate to HER2-targeted treatment regimens is not significantly high, suggesting the necessity for additional research to discover more efficient treatment approaches for this specific subgroup of colorectal cancer patients (42). Another study compared the efficacy and safety of third-line treatments for metastatic colorectal cancer, including regorafenib, TAS-102, and trifluridine-tipiracil. Regorafenib plus nivolumab improved overall survival compared to placebo plus best supportive care in CRC patient treatment and management (43). A study also discusses advanced colorectal cancer treatments and suggests using PARP inhibitors like veliparib with FOLFIRI was a more effective treatment (44). These studies suggest that CRC patients need a targeted, comprehensive therapy approach to improve results. Understanding the genetic landscape of CRC and discovering biomarkers like LOX-1 and CD8 can improve therapy regimens. Oncolytic viruses and immune checkpoint inhibitors have shown encouraging overall and progression-free survival, suggesting immunotherapy may be effective in CRC treatment.

The current review on colorectal cancer and its microenvironment also highlighted key findings that can optimize therapeutic strategies and found that the rational design of combination therapies, particularly optimizing immunotherapy and combination treatments, emerged as promising among all. Leveraging multiple treatment modalities may

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enhance efficacy and improve patient outcomes, as observed in studies. Additionally, patient selection criteria for targeted therapies were identified as crucial, emphasizing the importance of molecular targets and personalized approaches in treatment decision-making, supported by studies. Addressing drug resistance through adaptive treatment regimens or novel drug combinations is essential for long-term treatment success, as echoed in studies. Developing predictive models for treatment response by utilizing combination therapy and immune checkpoint inhibitors aims to enhance treatment outcomes by predicting patient responses more accurately, supported by studies. These findings align with other relevant studies on colorectal cancer, emphasizing the complex interplay between therapeutic strategies, patient characteristics, and the tumor microenvironment. Furthermore, a separate study has demonstrated the importance of directing therapeutic efforts toward the tumor microenvironment, namely by addressing immune responses, stromal cells, and signaling pathways. Colorectal cancer (CRC) is a highly widespread and lethal disease that affects people worldwide. Emerging evidence indicates that tumor-associated macrophages play a crucial role in the development of colorectal cancer (CRC), although the specific mechanisms by which they contribute to this process are still not fully understood (45). Similarly, another study found that the components of the tumor microenvironment initially have an anti-tumor effect but later become tumor growth promoters and favor cancer growth, local tissue invasion, and distant metastasis. This shows their importance in developing a promising treatment target, but it needs more study (46). Furthermore, researchers have shown a preference for cancer immunotherapy over conventional therapeutic choices like chemotherapy, surgery, and radiotherapy, taking into account specific patient characteristics and molecular profiles that have been identified as crucial for maximizing therapeutic advantages and reducing negative side effects of treatment (47).

Research limitations or gaps

CRC pathogenesis entails a considerable understanding gap concerning the synergistic impact of heritable mutations and environmental exposures. What is more, research must be future-oriented, investigating how genetic predisposition and environmental exposure interrelate to exert influence on the etiology and progression of CRC. Such action would unravel important disease mechanisms as well as determine populations at risk hence rendering prevention strategies more focused.

In addition, there should be studies that can follow up on therapy so as to ascertain whether it is effective or not after a certain period of time. It is necessary to know the outcome of patients in relation to treatment side effects and the length of response. Although some biomarkers predicting response have been identified previously, clinical usefulness should be confirmed using large cohort studies across different population groups in order for them to be incorporated effectively into personalized treatment programs.

Also, separation exists between comprehension of tumor microenvironment (TME) dynamics and CRC with respect to time. The overall implication behind molecular bases of assaying biomarkers remains vague too. This information is important for optimization of therapy regimens thus maximizing efficacy while minimizing toxicities especially in multiple drug therapies as well as targeted agents for CRC management purposes. Surgical interventions will facilitate personalization leading to better results both curative and palliative.

Conclusion

The comprehensive review reveals a multifactorial nature of pathogenesis, progression dynamics, therapeutic responses, and treatment outcomes of CRC. The diversity in found study designs, sample sizes, and publication years emphasize the rapid progression of research in this field. The review also shows that genetic mutations, environmental risk factors, immune cells, stromal cells, and extracellular matrix components played an important role in CRC pathophysiology and tumor microenvironment modulation. Moreover, cell-cell interactions, paracrine signaling, immune evasion mechanisms, and therapeutic responses highlighted the complexity of CRC biology and the treatment landscape. The study also emphasizes adopting a holistic approach to CRC management, integrating insights from genetics, environmental factors, immune responses, and treatment modalities. Personalized treatment strategies, combination therapies, targeted approaches, and predictive modeling, are important for optimizing therapeutic efficacy and mitigating drug resistance. There is a necessity for continued research and clinical exploration to unravel the complexities of CRC, advance treatment paradigms, and ultimately improve patient outcomes.

Authors' Contributions

All authors participated in formulating the concept, executing the implementation, processing the results, and composing the manuscript.

Ethical Considerations

Ethical approval is not necessary for this type of study.

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Declared none.

Conflict of Interests

The authors declare that they have no competing interests.

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