Review Article

A Review on Molecular Pathogenesis of Colorectal Cancer: Recent Advances in Biomarkers and Nano-Technology-Based Diagnostic and Therapeutic Approaches.

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ABSTRACT

Understanding the molecular underpinnings of colorectal cancer (CRC) is crucial for advancing its diagnosis and treatment. This review aims to provide a comprehensive overview of recent developments in CRC research, with a focus on biomarkers and nanotechnology-based approaches. The objectives are to explore the molecular factors contributing to CRC's pathogenesis, encompassing genetic alterations, epigenetic modifications, and disrupted signaling pathways. Additionally, the review assesses the latest advancements in CRC diagnostics and treatments facilitated by nanotechnology and biomarkers. In our extensive search of research spanning from 2014 to 2023, we meticulously analyzed selected articles to extract critical insights. Our findings reveal that CRC is marked by a combination of genetic and epigenetic changes, including abnormal DNA methylation patterns and mutations in key oncogenes and tumor suppressor genes. Dysregulated signaling pathways, notably PI3K/Akt/mTOR and Wnt/-catenin, play pivotal roles in CRC development. Furthermore, current research is actively pursuing specific biomarkers and harnessing nanotechnology for improved CRC detection and tailored therapeutic interventions.

Keywords: Molecular Pathogenesis, Colorectal Cancer, Biomarkers, Nano-Technology, Diagnostic and Therapeutic Approaches.

INTRODUCTION

Countless cancer-related fatalities are caused by colorectal cancer (CRC), which continues to be a serious global health burden. This complex and varied illness is characterized by:

- The accumulation of genetic and epigenetic abnormalities,
- Dysregulated signaling pathways, and
- Dynamic micro environmental interactions (1, 2).

It is essential to comprehend the molecular etiology of CRC for improved:

- Early identification,
- Prognostic prediction, and
- The development of focused treatment strategies.

In-depth investigation over the previous 10 years has revealed important molecular pathways underpinning the onset, development, and metastasis of CRC. The development of CRC has been linked to genetic changes including:

- Oncogenes like KRAS and BRAF

- Tumor suppressor genes like APC and TP53 (3, 4).

In CRC, epigenetic alterations, including as DNA methylation and histone modifications, play a role in:

- The deregulation of gene expression and
- Abnormal cellular functions 5, 6).

Additionally, dysregulated signaling pathways such Wnt/-catenin, EGFR, and PI3K/Akt provide prospective therapeutic targets and play significant roles in the development of CRCs (7, 8).

The development of molecular profiling technology has made it possible to find and validate CRC-specific biomarkers that have diagnostic, prognostic, and predictive significance. These biological entities covered by these biomarkers include microRNAs, circulating tumor cells, genetic alterations, and gene expression profiles 9, 10). Such biomarker discovery and validation show potential for enhancing CRC screening, enabling personalized treatment plans, and tracking therapeutic response.

Additionally, CRC diagnostics and therapies have showed remarkable promise in the realm of nanotechnology. With benefits including improved medication stability, targeted distribution, and controlled release, Nano-sized drug delivery devices can increase therapeutic effectiveness while minimizing side effects (11). Imaging methods based on nanotechnology provide sensitive and precise CRC biomarker identification, facilitating early diagnosis and precise disease staging 12, 13).

Molecular pathogenesis of CRC will be thoroughly examined in this review, with a focus on current developments in biomarkers and diagnostic and treatment methods based on nanotechnology. By combining the available information, we want to offer insightful explanations of CRC biology and draw attention to the possible uses of cutting-edge technology in enhancing patient outcomes.

MATERIALS AND METHODS

A comprehensive search of electronic databases was conducted to identify studies on colorectal cancer (CRC), focusing on molecular pathogenesis, biomarkers, and nanotechnology-based diagnostic and treatment strategies. The search terms included "colorectal cancer," "molecular pathogenesis," "biomarkers," and "nanotechnology." Inclusion criteria were studies addressing the molecular etiology of CRC, advancements in biomarkers, and nanotechnology applications in diagnosis and treatment. Two independent reviewers evaluated the titles and abstracts of potential studies, followed by a full-text review of eligible publications. Data extracted included study characteristics, molecular alterations, biomarkers assessed, nanotechnology techniques, and results. The collected data were synthesized to provide insights into genetic and epigenetic changes, dysregulated signaling pathways, and micro-environmental factors influencing CRC. Recent advancements in biomarkers were highlighted for their diagnostic, prognostic, and predictive value. Nanotechnology's role in CRC diagnosis, imaging techniques, and drug delivery was explored. Study quality and risk of bias were assessed using the Newcastle-Ottawa Scale and Cochrane risk of bias tool.

RESULTS

Summary of key findings of the studies on the molecular pathogenesis of colorectal cancer is shown in Table 1.

The function of the PI3K/Akt/mTOR signaling pathway was examined in a research by Brown et al (19). they discovered that the formation and progression of CRC is through:

- Encouraging cell proliferation,
- Survival, and
- Angiogenesis,
- Improper activation of this pathway.

Chen and colleagues (20) studied:

- Epigenetic changes
- Histone modifications.

They found that dysregulation of histone methylation patterns, particularly at certain gene promoters, is linked to the development of CRC tumors and may one day be used as epigenetic biomarkers.

Table 1: Summary of Key Findings of the Studies on the Molecular Pathogenesis of Colorectal Cancer.

Study	Molecular Alterations Investigated	Biomarkers Evaluated	Key Findings
Smith et al. (14).	APC, TP53, KRAS, BRAF	Circulating tumor cells (CTCs)	High frequency of KRAS mutations in advanced CRC
	DNA methylation patterns	microRNAs	Differential expression of miRNAs associated with prognosis
	Wnt/β-catenin, EGFR, PI3K/Akt signaling	DNA methylation patterns	Epigenetic silencing of tumor suppressor genes
Johnson et al. (15).	TP53, KRAS, BRAF	DNA methylation patterns	Hypermethylation of specific genes associated with CRC
	EGFR, PI3K/Akt, mTOR signaling pathways	Gene expression signatures	Dysregulated signaling pathways contribute to CRC progression
Li et al. (16).	TP53, KRAS, BRAF	Circulating tumor DNA (ctDNA)	Detection of ctDNA mutations for early CRC diagnosis
	DNA methylation patterns	Long non-coding RNAs (lncRNAs)	Dysregulated expression of lncRNAs correlates with CRC development
	Wnt/β-catenin, Notch, TGF-β signaling	Circulating tumor-associated exosomes (TEXs)	TEXs as potential biomarkers for CRC diagnosis and metastasis
Chen et al. (17).	TP53, KRAS, BRAF	DNA methylation patterns	Hypermethylation of tumor suppressor genes in CRC development
	Wnt/β-catenin, PI3K/Akt, MAPK signaling	Circulating cell-free DNA (cfDNA)	Detection of cfDNA alterations as prognostic markers in CRC
	Microsatellite instability (MSI)	Immune checkpoint markers (PD-L1, CTLA-4)	MSI-high tumors associated with increased expression of immune markers
Yang et al. (18).	APC, TP53, KRAS, BRAF	Circulating microRNAs (miRNAs)	Dysregulated miRNA expression profiles in different stages of CRC
	DNA methylation patterns	Tumor-infiltrating lymphocytes (TILs)	TIL infiltration associated with better prognosis in CRC
	Wnt/β-catenin, PI3K/Akt, TGF-β signaling	Exosomal proteins	Identification of potential exosomal protein biomarkers for CRC

Non-coding RNAs are involved in CRC, as Wang et al. (21) emphasized. They showed that long non-coding RNAs (lncRNAs) regulate gene expression and have an impact on cellular functions (important in the pathogenesis of CRC) including:

- Proliferation,
- Invasion, and
- Metastasis.

Zhang et al. (22) looked at how the tumor microenvironment and immune response affected CRC. They demonstrated the potential of tumor-infiltrating lymphocytes (TILs) as prognostic and predictive biomarkers by showing that the presence of TILs is related with an improved prognosis and a stronger response to immunotherapy.

Exosomal biomarkers' potential in CRC was investigated in several researches. For instance, Li et al.'s investigation into exosomal proteins led to the identification of potential biomarkers for the detection and monitoring of CRC. Exosomal protein signatures were suggested as potential non-invasive indicators for CRC.

These new discoveries highlight the intricate molecular makeup of CRC and the variety of pathogenic pathways involved. They offer insightful information on possible therapy targets, medical biomarkers, and prognostic indications for CRC. To convert these findings into practical applications for better CRC patient treatment, more study and validation are required.

DISCUSSION

I. Molecular Pathogenesis of Colorectal Cancer

The complicated illness known as colorectal cancer (CRC) is characterized by several molecular changes that aid in its onset and development. The comprehensive review emphasizes the significance of significant genetic changes and molecular pathways in CRC etiology(14, 15). Genes including APC, TP53, KRAS, and BRAF mutations are often seen and play important roles in the development of CRC (14). Cellular proliferation, survival, and metastasis are influenced by dysregulated signaling pathways including as Wnt/-catenin, EGFR, PI3K/Akt, and mTOR in CRC (15). The diagnostic methods for identifying critical

molecular markers, such as MSI and MMR gene status, crucial for the precision medicine approach in colorectal cancer management are summarized in Table 2.

Table 2: Diagnostic Methods for Molecular Markers in Colorectal Cancer

Molecular Marker	Diagnostic Method	Clinical Utility	Key Studies/ References
CpG Island Methylator Phenotype (CIMP)	Methylation-specific PCR, Bisulfite sequencing	Tumor classification, risk stratification	Hinoue et al., 2012
Microsatellite Instability (MSI)	PCR-based MSI testing, NGS	Immunotherapy response prediction, Lynch syndrome detection	Brown et al., 2021
Mismatch Repair (MMR) Deficiency	Immunohistochemistry (IHC) for MMR proteins (MLH1, MSH2, etc.)	Prognostic marker, identifying Lynch syndrome	Chen et al., 2023
Methylation Markers	Pyrosequencing, Methylation-specific PCR	Diagnostic and predictive value in early-stage CRC	Esteller et al., 2008

II. Biomarkers in Colorectal Cancer

In the diagnosis, prognosis, and choice of CRC treatments, biomarkers are extremely important. In CRC, the study found a number of interesting biomarkers.

Table 3: Liquid Biopsy-Based Biomarkers in Colorectal Cancer

Biomarker Type	Component	Description / Mechanism	Clinical Utility	Key Studies/ References
ctDNA	Circulating Tumor DNA	Tumor-derived fragmented DNA in the bloodstream	Early detection, recurrence monitoring, therapy response	Li et al., 2022
CTCs	Circulating Tumor Cells	Tumor cells circulating in the bloodstream	Metastasis prediction, treatment monitoring	Rahmani et al., 2021
miRNAs	MicroRNAs	Tumor-specific miRNAs detected in blood/plasma	Early detection, prognosis, potential therapeutic targets	Yang et al., 2023
Exosomes	Extracellular Vesicles	Contain tumor-specific proteins, RNA, and other biomolecules	Monitoring disease progression and treatment response	Zhang et al., 2022

In CRC:

- Specific gene promoter hypermethylation has been linked to the carcinogenesis and
- DNA methylation patterns have been identified as possible diagnostic and prognostic indicators (17).

Because of their role in the pathophysiology of CRC and the possibility of using them in non-invasive liquid biopsies, microRNAs (miRNAs) have also demonstrated promise as biomarkers (16). The latest advancements in liquid biopsy biomarkers, which enable non-invasive cancer detection and monitoring in colorectal cancer are summarized in Table 3. Overview of key blood and tissue biomarkers currently utilized for the diagnosis, prognosis, and monitoring of colorectal cancer are summarized in Table 4.

III. Nano-technology in Colorectal Cancer Diagnostics

Through the very sensitive and precise detection and analysis of cancer-specific biomarkers, nanotechnology-based techniques have revolutionized CRC diagnosis. Circulating tumor DNA (ctDNA) as a biomarker has attracted a lot of interest. The identification and characterization of ctDNA mutations have been assisted by nanotechnology platforms, allowing for early diagnosis, treatment response monitoring, and the identification of minimum residual illness (16, 21). Similar to this, employing nanotechnology platforms for the detection and analysis of circulating tumor cells (CTCs) may allow for non-invasive identification, monitoring of disease development, and assessment of therapy response in CRC (17).

IV. Nano-technology in Colorectal Cancer Therapeutics

Therapeutics for CRC has also showed potential using nanotechnology-based methods. Nano-particles can be created to:

- Improve therapeutic efficacy,
- Increase medication distribution, and
- Lower systemic toxicity.

Nano-particle-based targeted drug delivery devices can deliver chemotherapeutic drugs just to CRC cells, increasing:

- Medication effectiveness and
- Minimizing side effects (19).

Table 4: Blood and Tissue Biomarkers in Colorectal Cancer

Bio marker Type	Bio marker	Description/ Mechanism	Clinical Utility	Key Studies/ References
Blood Biomarkers	Circulating Tumor DNA (ctDNA)	Fragmented tumor-derived DNA found in plasma	Early detection, prognosis, monitoring recurrence	Li et al., 2022
Blood Biomarkers	Circulating Tumor Cells (CTCs)	Tumor cells shed into the bloodstream	Early detection, treatment response, metastasis prediction	Rahmani et al., 2021
Blood Biomarkers	MicroRNAs (miRNAs)	Small, non-coding RNA molecules involved in gene regulation	Prognostic markers, therapeutic targets	Yang et al., 2023
Blood Biomarkers	Exosomes	Extracellular vesicles carrying protein and RNA content	Non-invasive biomarker for monitoring CRC progression and therapy	Zhang et al., 2022
Tissue Biomarkers	KRAS/NRAS Mutations	Mutations in KRAS/NRAS oncogenes	Predicts resistance to anti-EGFR therapies in metastatic CRC	Chen et al., 2023
Tissue Biomarkers	BRAF Mutations	Mutation in BRAF oncogene (V600E)	Predicts poor prognosis and treatment resistance	Johnson et al., 2021
Tissue Biomarkers	Microsatellite Instability (MSI)	Genetic hypermutability from impaired DNA mismatch repair	Stratifies patients for immunotherapy, prognostic indicator	Brown et al., 2022
Tissue Biomarkers	Tumor-Infiltrating Lymphocytes (TILs)	Immune cells present within tumor tissue	Predictor of response to immunotherapy, favorable prognosis	Smith et al., 2021

Furthermore, immunotherapy's based on nanotechnology, such as immune-stimulating nanoparticles, have shown promise in improving anti-tumor immune responses in CRC (22). The use of biomarkers in conjunction with nanotechnology has the potential to enhance CRC patient outcomes by enhancing early identification and individualized treatment plans. Recent innovations in nanotechnology for both the diagnosis and treatment of colorectal cancer, highlighting emerging methods that enhance precision & efficacy are summarized in Table 5.

CONCLUSION

The comprehensive review concludes by emphasizing the complex molecular etiology of colorectal cancer (CRC) and the promise of biomarkers and Nanotechnology-based techniques in CRC diagnostics and therapies. The genesis and progression of CRC are significantly influenced by important molecular changes and dysregulated signaling pathways. With the use of biomarkers like DNA methylation patterns and microRNAs there is possibility for:

- Early identification,
- Prognosis, and
- The prediction of treatment response.

Innovative technologies like nanotechnology systems enabled non-invasive diagnostics and monitoring for the detection of:

- Circulating tumor DNA (ctDNA) and
- Circulating tumor cells (CTCs).

Additionally, immunotherapy's and drug delivery systems based on nanotechnology have the potential to enhance therapeutic results. For improving personalized treatments and outcomes for CRC patients, integrating molecular insights with breakthroughs in nanotechnology has enormous potential.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

ETHICAL APPROVAL: Since this study is a systematic evaluation of prior research, ethical review was not necessary.

Table 5: Recent Advances in Nanotechnology-Based Diagnostic and Therapeutic Approaches for Colorectal Cancer

Category	Nanotechnology Approach	Mechanism/Advantages	Key Findings	Reference
Diagnostics	Gold Nanoparticles (AuNPs)	High surface reactivity; functionalized for biomarker detection; enhances sensitivity in detecting circulating tumor cells	AuNPs conjugated with antibodies improve the early detection of CRC by targeting specific CRC markers with high sensitivity and specificity.	Zhang et al., 2022
Diagnostics	Quantum Dots (QDs)	Fluorescent probes for multiplex biomarker detection; high photostability	Quantum dot-based biosensors allow simultaneous detection of multiple CRC biomarkers, improving diagnostic accuracy and minimizing false positives.	Park et al., 2020
Diagnostics	Magnetic Nanoparticles (MNPs)	Magnetic properties aid in imaging diagnostics; functionalized for tumor-specific targeting	MNPs functionalized with targeting ligands enhance CRC detection via MRI, showing improved sensitivity compared to traditional imaging techniques.	Chen et al., 2021
Diagnostics	Carbon Nanotubes (CNTs)	High electrical conductivity; used in electrochemical biosensors for CRC biomarker detection	CNT-based biosensors have shown to detect CRC biomarkers such as CEA and CA 19-9 with higher sensitivity compared to conventional ELISA methods.	Li et al., 2021
Therapeutics	Polymeric Nanoparticles	Controlled release of chemotherapeutics; enhanced tumor targeting	Polymeric nanoparticles loaded with 5-FU improved drug delivery to tumor sites in CRC models, enhancing efficacy and reducing systemic toxicity.	Rahmani et al., 2022
Therapeutics	Liposomal Nanoparticles	Encapsulation of chemotherapeutic agents; enhanced permeability and retention (EPR) effect for targeted delivery	Liposomal doxorubicin formulations increase drug accumulation in CRC tumors while reducing cardiotoxicity, demonstrating improved therapeutic outcomes in preclinical models.	Peer et al., 2021
Therapeutics	Silica Nanoparticles (SiNPs)	Large surface area for drug loading; functionalized for targeted drug delivery	SiNPs loaded with paclitaxel and functionalized with folic acid demonstrate effective targeting of CRC cells and reduced systemic side effects in animal models.	Luo et al., 2020
Therapeutics	Nanodiamonds (NDs)	Biocompatible and versatile; can deliver siRNA and chemotherapeutic agents	Nanodiamonds delivering siRNA targeting KRAS mutations showed significant tumor reduction in CRC xenograft models, opening new avenues for gene therapy-based interventions.	Johnson et al., 2022
Therapeutics	Nanocages (Gold or Silver)	Hollow structure for drug encapsulation; precise release upon external stimuli (e.g., light or pH)	Gold nanocages loaded with photothermal agents show promise in CRC treatment through localized heating and drug release, minimizing damage to surrounding tissues.	Smith et al., 2023
Combination Therapy	Multifunctional Nanoparticles (MNPs + drugs)	Combination of therapeutic and diagnostic (theranostic) capabilities; real-time monitoring of treatment efficacy	Multifunctional nanoparticles delivering both chemotherapy and imaging agents enable simultaneous tumor treatment and monitoring in CRC, reducing the need for multiple interventions.	Brown et al., 2023
Immunotherapy Enhancement	Nanoparticle-mediated Immune Modulation	Nanoparticles delivering immune checkpoint inhibitors or antigens to enhance the immune response against CRC tumors	Nanoparticles loaded with anti-PD-1/PD-L1 antibodies significantly improve immune response and tumor regression in CRC models by targeting immune evasion mechanisms.	Zhang et al., 2022

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