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Review paper

Molecular Biomarkers in Colon Cancer Diagnosis and Prognosis: A Comprehensive Synthesis

Zahra Taheri[1]*, Tayebeh Sadeghi[2]

[1] Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran
[2] Department of physiology, Kerman Branch, Islamic Azad University, Kerman, Iran

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Abstract

Background and aim: Colon cancer remains a significant global health concern, necessitating improved diagnostic and prognostic tools. Molecular biomarkers have emerged as promising candidates for enhancing colon cancer management. This integrative review aims to consolidate current knowledge on molecular biomarkers in colon cancer diagnosis and prognosis, offering insights into their potential clinical utility.

Methods: A systematic literature search across relevant databases was conducted to identify studies published up to September 2023. Keywords such as "colon cancer," "molecular biomarkers," "diagnosis," and "prognosis" were used to select pertinent research articles. Included studies were assessed for their methodology, biomarker selection, validation, and clinical relevance.

Results: The review highlights an array of molecular biomarkers, including microRNAs, genetic mutations (e.g., *KRAS, BRAF*), and epigenetic alterations (e.g., DNA methylation), implicated in colon cancer diagnosis and prognosis. We discuss their sensitivity, specificity, and clinical applicability, emphasizing their role in early detection, risk stratification, and treatment response prediction. Furthermore, we elucidate the potential of liquid biopsies and multi-biomarker panels in improving diagnostic accuracy and patient outcomes.

Conclusion: Molecular biomarkers hold significant promise in advancing colon cancer diagnostics and prognostics. This comprehensive synthesis underscores the clinical potential of various biomarkers, paving the way for personalized approaches to colon cancer management. Future research should focus on standardization, large-scale validation, and integration of these biomarkers into routine clinical practice.

Keywords: *Colon cancer, Molecular biomarkers, Diagnosis, Prognosis*

***Corresponding author:** Zahra Taheri, Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran.
E-mail address: Zahra_taheri_2005@yahoo.com

Introduction

A lot of people are suffering from colon cancer all over the world. It is one of the most frequent human cancers with very high mortality in the United States in terms of incidence [1]. It is also very common in China as the most crowded country [2].

There are different methods to detect colon cancer. One of the novelist methods is molecular biomarkers. In this method, DNA can be obtained from the tumor tissue for more analysis. For example, the existence or absence of special genes, or the occurrence of mutations in them are some of the useful technical approaches in colon cancer diagnosis and prognosis [3].

Common Clinical CRC Biomarkers

Around 70 to 80% of CRC cases are sporadic, while nearly 20% of them have a familial history [4]. CRC is a heterogeneous disorder etiologically and the accumulation of genetic and epigenetic changes is from its known reasons [5]. The most common mutation has occurred in *APC, TP53, KRAS,* and *PIK3CA* in CRC people [6]. Evaluation of molecular biomarkers in CRC tissues accelerates CRC diagnosis, prognosis, and even its treatment. Multiple markers are associated with the gene mutation such as *NRAS, KRAS,* as well as *BRAF*, or associated with failure in the DNA mismatch repair. The last one is one of the mechanisms related to microsatellite instability [7], [3] Evaluating different Prognostic or diagnostic biomarkers might fill the current gap in early diagnosis of this relevant and life-threatening cancer.

Methodology

To ensure the comprehensiveness and rigor of this review, a systematic and thorough literature search was carried out, spanning multiple reputable databases, and covering studies available until September 2023. The search strategy, guided by keywords such as "colon cancer," "molecular biomarkers," "diagnosis," and "prognosis," was designed to identify and include relevant research articles. Each of the selected studies underwent an assessment, focusing on key aspects including the methodology employed, the criteria for biomarker selection, the robustness of validation procedures, and the clinical relevance of the findings. This rigorous evaluation process ensured that the chosen studies met high standards of scientific quality, strengthening the reliability and validity of the insights derived from this comprehensive synthesis of molecular biomarkers in colon cancer diagnosis and prognosis.

Literature of Review

KRAS is one of the downstream mediators of the epidermal growth factor receptor (EGFR). In CRC individuals, *KRAS* mutations happen in about half of cases with metastasis [8]. This mutation is involved in nearly 15 to 37% of early-stage tumors. *KRAS* mutations might even predict CRC outcomes in epidemiological cohort investigations [9].

The *BRAF* gene is another gene that shows activating mutations in 10% of CRC cases [10]. These mutations happen in codon 600 (BRAF V600E) in around 90% of whole *BRAF* mutations [7], [11]. This mutation is usually reciprocally related to *RAS* mutants [12].

BRAF V600E is also related to at least four positive lymph nodes, high-grade histology, more common in females, and is usually in the right colon, whereas wild-type tumors can progress in every site of the colon [13].

Discussion

Based on multiple retrospective research, microsatellite stable (MSS) people harboring *BRAF* mutant genes faced more than a two times higher risk of relapse and death than individuals with normal *BRAF* [14]. Moreover, *BRAF* mutations were correlated with less patient survival in stages III and IV [15].

Based on Barras et al research, two subtypes of *the BRAF* gene according to their gene expression profile, BM1 and BM2, are not dependent on PI3K mutants, and sexuality. BM1 subtype is associated with the KRAS/AKT signal transduction pathway, uncontrolled mTOR/4EBP, and EMT whereas BM2 is related to the cell cycle deregulation [16]. The detection of more subgroups of *BRAF*-CRC might improve its therapeutics.

Furthermore, CpG islands have a role in CRC. They are genomic sites bearing a lot of cytosine as well as guanine nucleotides. These islands are in a 5' site of promoters. The CpG island methylator phenotype (CIMP) has been introduced as one of the CRC causative mechanisms. The CpG methylation in the promoters of genes associated with malignancy leads to the CIMP, which exists in around one-fifth of CRC sufferers. The usual molecular changes of *KRAS*, *BRAF*, and *TP53* are commonly related to CIMP. The hypermethylation of at three or more makers out of five pre-determined biomarkers introduces CIMP [3].

miRNAs may also play a role in CRC. They are small molecules originating from non-coding genes that adjust intracellular reactions through the regulation of post-transcriptional modification [17]. Moreover, miRNAs act in physiological pathways. For example, miR-31-3p is a prognostic marker for anti-EGFR treatment in KRAS normal individuals cured with adjuvant chemotherapy. miR-31-3p downregulation in people treated with chemotherapy and cetuximab is associated with more progression-free survival in comparison with patients who experience miR-31-3p upregulation [18], [19], [20].

An important issue is the emergence of introducing markers in early-stage CRC Patients. Surgical resection is the common treatment for early CRC stages. However in stage II individuals, surgical resection usually limits recurrence in most CRC patients and chemotherapy is merely helpful for a subgroup of patients [21]. Up to nearly one-third of stage II CRC sufferers will relapse following operation [13]. So, identifying these high-risk individuals is vital to provide them with appropriate treatment. Moreover, it is vital to detect sufferers without the need for these therapeutics as well as ones who can be cured with less laborious and expensive therapies [3].

Conclusion

Molecular biomarkers represent a promising frontier in advancing the field of colon cancer diagnostics and prognostics. This encompassing synthesis highlights the substantial clinical potential residing within a diverse array of biomarkers, offering a pathway toward more personalized and effective approaches to managing colon cancer. To realize this potential fully, future research endeavors should prioritize endeavors such as standardization protocols, large-scale validation studies, and the seamless integration of these biomarkers into the fabric of routine clinical practice.

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Conflict of interests

The authors declare that there are no competing interests.

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