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Review article

ANALYSIS OF TP53, APC, KRAS, AND MMR GENETIC MUTATIONS IN COLORECTAL CANCER: A REVIEW ARTICLE

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Abstract: **Introduction:** Colorectal cancer (CRC) is one of the most common malignancies with significant global health and economic implications. Genetic mutations in genes such as TP53, APC, KRAS, and MMR play a crucial role in the development and progression of this cancer. This review paper analyzes current knowledge about the impact of these mutations on colorectal carcinogenesis, using available literature.

Objective: To provide a comprehensive review of the role of genetic mutations in TP53, APC, KRAS, and MMR genes in the development of colorectal cancer and to consider their impact on diagnosis and treatment.

Materials and Methods: This review examines peer-reviewed research articles and reports sourced from databases such as PubMed, Google Scholar, and other academic sources. The focus was on studies investigating genetic mutations, their prevalence, and their role in the pathogenesis of CRC.

Results: Mutations in the TP53 gene, present in more than 50% of CRC cases, are critical for malignant cell transformations. KRAS mutations, found in about 50% of cases, lead to abnormal signaling contributing to unchecked proliferation. APC mutations are associated with hereditary predisposition to CRC, while MMR genes, such as MLH1 and MSH2, play a key role in DNA repair and are linked to hereditary nonpolyposis colorectal cancer.

Conclusion: Genetic mutations in TP53, APC, KRAS, and MMR genes play a significant role in the development of colorectal cancer. A deeper understanding of these mutations may significantly enhance diagnostic and therapeutic strategies, guiding future research in this rapidly evolving field.

Keywords: Colorectal Neoplasms, Carcinogenesis, Mutation, Genes, Tumor Suppressor.

INTRODUCTION

Colorectal carcinoma (CRC) is a malignant tumor that originates in the epithelium of the colon and rectum. According to recent statistical data, the incidence of CRC in this region shows a decline, but the mortality rate remains high, indicating the need for improved prevention, diagnosis, and treatment strategies (1).

The carcinogenesis of CRC is a complex process that typically develops from benign adenomas. Adenomas, which are precursors to carcinoma, undergo stages of dysplasia and hyperplasia before becoming malignant. During this process, a series of genetic and epigenetic changes occur, leading to malignant transformation (2). The mechanisms underlying these changes include mutations in specific oncogenes and tumor suppressor genes. The most important genes involved in the development of CRC are TP53, KRAS, APC, and those that are part of the DNA mismatch repair system (MMR genes such as MLH1, MSH2, MSH6, and PMS2) (3, 4).

TP53 encodes the tumor suppressor protein p53, whose functions include the regulation of the cell cycle and the induction of apoptosis in cells with damaged DNA. Mutations in the TP53 gene are associated with many types of tumors, including CRC (5). KRAS is an oncogene that plays a key role in cell signaling; its mutations can lead to abnormal cell proliferation and tumorigenic signaling (6). The APC gene is associated with familial adenomatous polyposis (FAP) and plays a role in regulating cell proliferation and apoptosis (7). MMR genes are responsible for recognizing and correcting errors in DNA during replication; their dysfunction leads to microsatellite instability (MSI) and increases the risk of CRC (8).

Although specific genetic mutations associated with CRC are well documented, significant gaps still

exist in understanding their roles and interactions (9). This review paper aims to identify unexplored areas, such as the impact of combinations of mutations and environmental factors, as well as unknown genetic variants that could play a role in the development of CRC.

AIM

To provide comprehensive insights into the genetic and molecular mechanisms involved in the development of colorectal carcinoma. This paper focuses on analyzing various genetic mutations and their roles in carcinogenesis, including genes associated with both hereditary and sporadic forms of CRC. Special emphasis is placed on exploring advanced mutation detection methods that enable precise diagnosis and personalized treatment for CRC patients. Understanding these mechanisms can contribute to improving strategies for early detection, prevention, and therapy of CRC, thereby significantly enhancing patient outcomes and reducing the associated mortality rate.

MATERIALS AND METHODS

This review paper relies on the analysis of available literature and previous research in the field of CRC. The material for analysis includes articles published in relevant medical and genetic journals, as well as data from clinical studies and meta-analyses.

Literature Review

Relevant bibliographic databases, including PubMed, Google Scholar, Scopus, and Web of Science, were used to identify key studies and peer-reviewed articles. The search was conducted using Boolean operators (AND, OR, NOT) to include relevant publications investigating the genetic aspects of CRC. The keywords used in the search included "colorectal carcinoma," "genetic mutations," "TP53," "KRAS," "APC," "MMR," "hereditary cancer," and "sporadic cancer." Additionally, relevant research in the field of meta-analysis addressing the prevalence and pathogenesis of CRC was explored.

Data Analysis and Synthesis

After identifying relevant studies, the data were analyzed to uncover key mechanisms and trends related to genetic mutations and their roles in CRC development. Qualitative analysis and synthesis methods were employed to review current knowledge and gaps in this area. Special attention was given to analyses that thoroughly examined the roles of genes such as TP53, KRAS, APC, and MMR in carcinogenesis. The analysis also included studies investigating advanced mutation detection methods, aiming to identify opportunities for precise diagnosis and personalized treatment for CRC patients.

RESULTS

Genetic Mutations and Their Frequency

The analysis of available literature and existing studies identified key genetic mutations that play a significant role in the development of CRC. These mutations affect various genetic pathways that contribute to carcinogenesis.

TP53

The cell cycle consists of several phases, with a key regulatory checkpoint at the transition from the G1 to the S phase. The tumor suppressor gene TP53, located on the short arm of chromosome 17 (position 13.1) (Figure 1), encodes the p53 protein, known as the "guardian of the genome" (5, 10). This protein plays a crucial role in regulating the cell cycle by activating genes responsible for DNA repair or apoptosis. Increased concentrations of p53 due to DNA damage cause cell cycle arrest, allowing for DNA repair or, if the damage is too severe, the initiation of apoptosis (10).

If mutations occur in the TP53 gene, the function of the p53 protein may be compromised, allowing the replication of damaged DNA during the S phase. Even a small change in a single amino acid can severely impair p53 function, leading to the accumulation of mutations and potentially the development of tumor cells. These mutations are present in more than 50% of all tumors, including a significant number of CRC cases (11).

KRAS

The KRAS gene encodes the K-RAS protein, which plays a key role in intracellular signaling. This protein is activated by binding to GTP and inactivated by hydrolyzing GTP to GDP. KRAS, located on chromosome 17p12.1, is one of the most frequently activated oncogenes (Figure 2). Mutations in this gene are detected in 17-25% of all tumors and are particularly prevalent in approximately 50% of CRC cases (12).

Under normal conditions, external signals stimulate the accumulation of GTP, which binds to K-RAS, activating it. K-RAS is then inactivated when GTP is converted to GDP, halting the signal (12). However, mutations in the KRAS gene, particularly in exons 12, 13, and 61, lead to reduced GTPase activity of the protein. These changes cause constant activation of K-RAS, disrupting cell cycle control and contributing

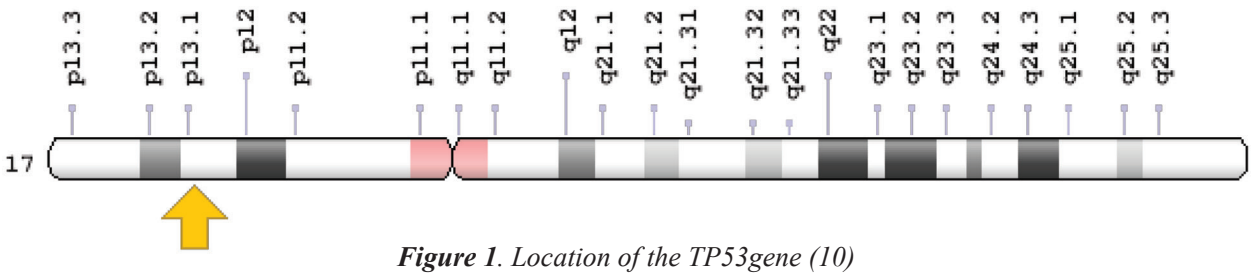

***Figure 1**. Location of the TP53gene (10)*

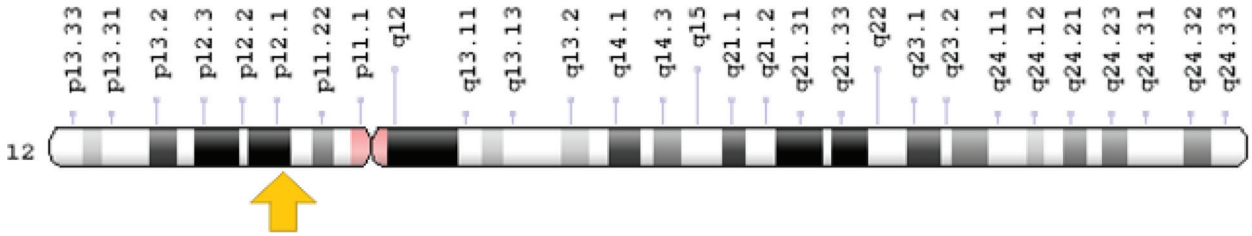

***Figure 2.** Location of the KRAS gene (12)*

to the abnormal karyotype known as chromosomal instability (CIN). K-RAS is also associated with disruptions in cytoskeleton organization during cell division, further contributing to CIN (13). Additionally, recent studies show that cells from patients with specific KRAS mutations are resistant to apoptosis that should be induced by chemotherapy. This finding indicates low chances of curing patients with KRAS mutations but also opens up opportunities for developing new therapeutic strategies (14).

APC

The APC gene, located on the long arm of chromosome 5 (5q22.2), encodes a protein that plays a key role in regulating the cell cycle, cell adhesion and migration, as well as chromosome segregation (Figure 2) (15). Mutations in this gene, including deletions, frameshift mutations, and point mutations, have been recorded in over 700 cases of individuals with familial adenomatous polyposis (FAP) (16).

Under normal conditions, the APC protein associates with the cytoskeleton, specifically microtubules, and is involved in spindle formation during cell division. When the APC gene functions properly, the APC protein, as part of a complex that includes other proteins, binds to β-catenin and phosphorylates it, signaling its degradation. However, in the presence of WNT signaling or in cases of a dysfunctional APC protein, β-catenin is not phosphorylated and translocates to the nucleus, where it activates the transcription of genes responsible for cell proliferation (Figure 3) (17).

This improper activation of β-catenin causes the constitutive expression of proliferation-related genes, contributing to the development of tumor cells. Mutations in the APC gene, therefore, play a significant role in the WNT/β-catenin signaling pathway, which regulates cell proliferation. In addition to APC mutations,

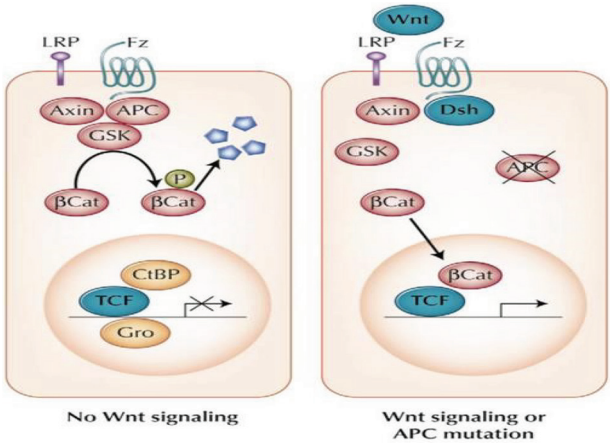

***Figure 3.** WNT/β-catenin Signaling pathway (17)*

a small number of CRC cases have also identified mutations in the CTNNB1, AXIN1, and AXIN2 genes, which encode proteins of this signaling pathway (18).

Chromosomal abnormalities associated with APC mutations contribute to the phenotype known as chromosomal instability, which is characteristic of many CRC cases. According to available data, the location of the mutation in the APC gene determines the number of polyps and the age at which they appear, providing key insights into the disease's progression(19).

MMR Genes

Mismatch Repair (MMR) genes, including MSH2, MLH1, PMS1, PMS2, MSH6, and MSH3, play a crucial role in recognizing and repairing mismatched bases during DNA replication (8). Mutations in these genes are the main cause of hereditary nonpolyposis colorectal cancer (HNPCC) syndrome and are also present in sporadic cases of CRC. The most common mutations occur in the MSH2 and MLH1 genes, while other genes are less frequently affected (20).

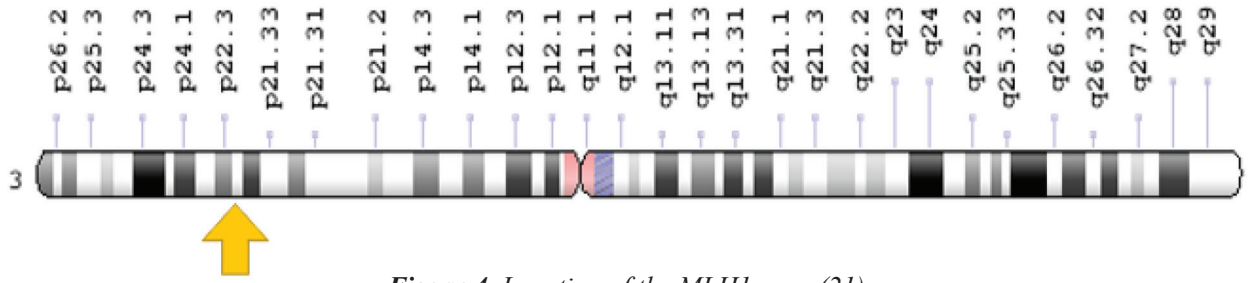

Figure 4. *Location of the MLH1 gene (21)*

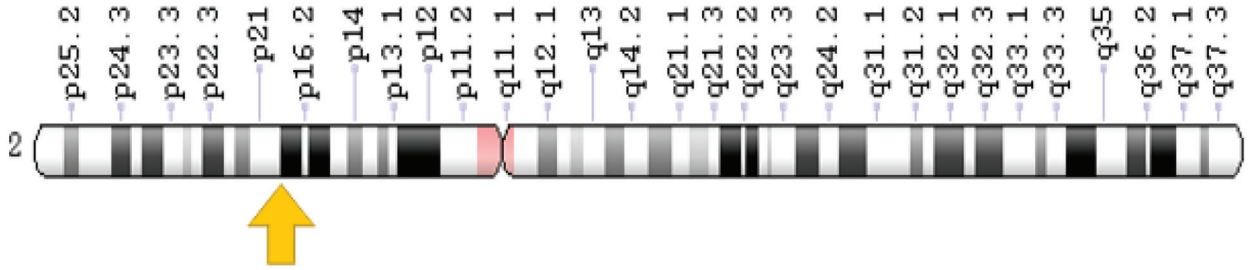

Figure 5. *Location of the MSH2 gene on the short arm of chromosome 2 at position 21(22)*

MLH1

The MLH1 gene, located on chromosome 3p21.3, encodes a protein that forms a complex with PMS2, which is essential for recognizing and repairing mismatched nucleotides (Figure 4). Mutations in MLH1 can cause HNPCC syndrome and variants such as Turcot syndrome and Muir-Torre syndrome. This gene plays a vital role in maintaining the accuracy of DNA replication (21).

MSH2

The MSH2 gene is located on chromosome 2 and encodes a protein that forms a complex with MSH6 or MSH3, enabling the identification of DNA errors (Figure 5). Mutations in MSH2 account for approximately 40% of HNPCC cases and are associated with various skin cancers (22).

EPCAM

The EPCAM gene encodes the epithelial cell adhesion molecule (EpCAM), a membrane protein that facilitates cell adhesion and can shed the intracellular domain (EplCD). Deletion of the 3' end of EPCAM leads to a truncated mRNA transcript and hypermethylation of the MSH2 promoter, resulting in reduced functional MSH2 protein. This mutation occurs in approximately 6% of HNPCC cases (23).

MUTYH

The MUTYH gene, located at position 34.1 on chromosome 1, encodes the MYH glycosylase enzyme, which is crucial for repairing oxidative damage to bases. Autosomal recessive mutations in this gene cause MUTYH-associated polyposis (MAP), which can lead to CRC. The most common mutations are tyrosine-cysteine (Tyr179Cys) and glycine-aspartic acid (Gly396Asp), present in 2% of the population but varying among ethnic groups (24).

SMAD4

The SMAD4 gene, located on chromosome 18, encodes a protein involved in the TGF-β signaling pathway, inhibiting cell growth and functioning as a tumor suppressor. Mutations in this gene lead to Peutz-Jeghers syndrome (PJS) and affect extracellular matrix protein synthesis, potentially contributing to metastasis and the development of sporadic CRC (25).

STK11

The STK11 gene, located on chromosome 19, encodes the tumor-suppressor enzyme serine/threonine kinase 11 (STK11), which regulates cell polarization, energy balance, and apoptosis. Hereditary mutations in STK11 cause Peutz-Jeghers syndrome, which is associated with an increased risk of CRC. Mutations in this gene can be deletions, insertions, or changes in the sequence, leading to functional protein disorders (26).

Advanced Detection Methods

With advancements in technology, various sophisticated methods have been developed for detecting genetic mutations associated with CRC. These methods enable precise identification of mutations and enhance diagnosis and personalized treatment.

Fluorescent In Situ Hybridization (FISH)

The FISH technique uses fluorescent probes that specifically recognize and bind to certain DNA sequences. This method allows visualization of chromosomal abnormalities and mutations at the cellular level. FISH is useful for identifying amplifications and deletions in genes such as HER2 in breast cancer and MYC in various tumor types, including CRC (27).

Comparative Genomic Hybridization (CGH)

The CGH technique allows for the detection of genetic changes such as amplifications, deletions, and other chromosomal aberrations. This method uses DNA hybridization of the sample with a reference genome on microarrays, enabling quantification and identification of genetic changes present in tumors, including CRC (28).

Allele-Specific PCR (AS-PCR)

AS-PCR is a method that allows for the detection of specific genetic mutations based on different alleles in DNA. This technique is highly precise and is used to identify specific mutations in genes such as KRAS and TP53, enabling personalized therapy and better management of CRC patients (29).

DNA Sequencing

DNA sequencing, including next-generation sequencing, allows for a detailed exploration of the genome and identification of all present mutations. This method provides a comprehensive overview of all variations in the genetic material, including rare and unknown mutations that may play a significant role in CRC development (30).

Shield Test

The Shield test is a blood test that utilizes a multimodal approach for early detection of CRC in individuals at average risk over the age of 45. This test integrates genomics, epigenomics, and proteomics to detect circulating tumor DNA (ctDNA) in the bloodstream, with a sensitivity of 91% for detecting CRC and 20% for advanced adenomas, and a specificity of 92%. Although it is not a replacement for standard methods, it could significantly increase the number of individuals participating in screening and thereby reduce CRC mortality. The clinical validation of the test was conducted through a large study called ECLIPSE (31).

DISCUSSION

This review aimed to provide a comprehensive overview of the genetic and molecular mechanisms contributing to the development of colorectal cancer (CRC), with a specific focus on analyzing genetic mutations and the application of advanced detection methods. The methodological approach employed facilitated a relevant review of current knowledge in this field.

The results of the analysis clearly indicate that mutations in the **TP53**, **KRAS**, **APC**, and **MMR** genes are central to understanding CRC carcinogenesis (32). These mutations not only contribute to the development of CRC but also provide valuable information for the diagnosis and treatment of the disease (33, 34, 35).

Mutations in the **TP53** gene, present in over 50% of CRC cases, have a profound impact on malignant cell transformation. The p53 protein plays a crucial role in regulating the cell cycle and responding to DNA damage. Loss of function of this protein allows cells to survive and proliferate despite genetic damage. Our analysis confirms previous findings regarding the role of TP53 in a broad spectrum of cancers, including CRC (11, 36, 37). However, further research is needed to elucidate the specific mechanisms through which TP53 mutations contribute to CRC development.

Mutations in the **KRAS** gene, particularly in exons 12, 13, and 61, are found in about 50% of CRC cases. KRAS is a key regulator of signaling pathways that affect cell growth and differentiation. Our analysis supports previous studies showing that abnormal signaling due to KRAS mutations contributes to uncontrolled cell proliferation. It is important to note that different KRAS mutations may have varying effects on tumors, which could influence therapeutic approaches (33, 38-41).

Mutations in the **APC** gene are associated with the development of familial adenomatous polyposis (FAP) and contribute to chromosomal instability that can lead to malignant transformations. Our analysis confirms the role of APC mutations in CRC, consistent with previous work (42, 43). However, since APC mutations are often detected in later stages of the disease, there is a pressing need to explore early biomarkers that could enable timely recognition and intervention (31).

Mutations in the **MMR** genes, including **MLH1** and **MSH2**, are critical for hereditary nonpolyposis colorectal cancer (HNPCC). These mutations impair DNA mismatch repair and contribute to the accumulation of mutations that lead to tumor formation (44, 45). Although we confirmed the significance of MMR mutations, further research is necessary to better un-

derstand their role in different stages of CRC carcinogenesis (39).

One of the main limitations in current research is the lack of data on interactions between different genetic mutations and environmental factors. While some of these factors have been studied, many remain unexplored (46). Additionally, methodological variations across studies can affect results and complicate data comparisons.

To improve CRC diagnosis and treatment, future research should focus on several key areas. First, it is essential to identify new genetic variations that may play a role in CRC development. These novel variations could reveal previously unrecognized biomarkers, paving the way for the development of innovative and more effective therapeutic approaches (47).

Second, it is crucial to investigate the interactions between genetic predispositions and environmental factors. Understanding how these factors collectively influence CRC development can provide new insights essential for disease prevention and treatment (45).

Third, continuous advancements in detection technology, particularly in sequencing, can significantly enhance CRC diagnosis. The introduction of advanced technologies, such as next-generation sequencing (NGS), allows for more precise identification of genetic mutations and earlier disease detection. These technologies offer the potential to better understand tumor genetic profiles and tailor therapeutic approaches according to each patient's specific characteristics (48).

In addition to insights gained regarding genetic mutations in CRC, it is essential to consider the implications of these mutations on the choice of biological and immunotherapy. As our understanding of the molecular mechanisms underlying CRC evolves, targeted therapies are increasingly being developed to address specific genetic alterations (49).

For instance, the presence of KRAS mutations can influence the effectiveness of certain treatments. Patients with KRAS wild-type tumors may benefit from anti-EGFR therapies, while those with mutated KRAS do not typically respond to these agents (50). This highlights the necessity of genetic testing to guide treatment decisions, ensuring that patients receive the most appropriate therapy based on their tumor's genetic profile (49, 50).

Similarly, the role of MMR mutations in determining treatment strategies is becoming more evident. Patients with MMR-deficient tumors often exhibit higher levels of microsatellite instability (MSI), making them more responsive to immune checkpoint inhibitors such as pembrolizumab and nivolumab (51). Understanding the presence of MMR mutations thus not only aids in diagnosis but also provides critical information for selecting immunotherapeutic options that may lead to better patient outcomes (51).

Furthermore, ongoing research into the impact of TP53 and APC mutations on treatment responses is essential for developing more effective therapeutic strategies (52). TP53 mutations, often associated with poorer prognosis, can lead to resistance against standard chemotherapeutic agents. Understanding the specific pathways affected by these mutations may help identify alternative drugs or combination therapies that could improve patient outcomes (53).

Similarly, APC mutations, which contribute to tumorigenesis, may influence how tumors respond to targeted therapies. By investigating the molecular mechanisms behind these mutations, researchers can uncover potential biomarkers that predict treatment efficacy. This knowledge could guide oncologists in selecting the most appropriate therapies tailored to each patient's genetic profile, ultimately refining treatment protocols and enhancing the precision of CRC management (53, 54).

This review provides a comprehensive overview of the genetic mutations **TP53**, **APC**, **KRAS**, and **MMR** in the context of CRC, highlighting their pivotal roles in disease development and the potential implications for diagnosis and treatment. Understanding these mutations not only contributes to a better recognition of pathogenic mechanisms but also facilitates the development of personalized therapeutic approaches.

In addition to genetic factors, investigating the impact of these mutations on responses to biological and immunotherapy opens new therapeutic avenues. As specific interactions between genetic variants and treatment responses are elucidated, there is potential to enhance treatment protocols and optimize patient care.

Future research should prioritize the integration of genetic studies with clinical data and biostatistics. This multidisciplinary approach will enable deeper insights into the mechanisms of CRC and contribute to the development of innovative treatment strategies. Ultimately, the goal is to improve patient outcomes and reduce the global burden of this serious disease.

CONCLUSION

Understanding the genetic and molecular mechanisms contributing to colorectal cancer (CRC) development is fundamental for improving the diagnosis and treatment of this disease. Identifying specific mutations in genes such as **TP53**, **KRAS**, **APC**, and **MMR** enhances the management and treatment of CRC. Studying known genes and identifying new genetic factors responsible for carcinogenesis allows for

faster, more precise, and effective treatments for tumors, including colorectal cancer.

Abbreviations

CRC - Colorectal carcinoma
FAP - Familial adenomatous polyposis
MMR - Mismatch repair
HNPCC - Hereditary nonpolyposis colorectal cancer
TP53 - Tumor protein p53
KRAS - Kirsten rat sarcoma viral oncogene homolog
APC - Adenomatous polyposis coli
MLH1 - MutL homolog 1
MSH2 - MutS homolog 2
MSH6 - MutS homolog 6
PMS2 - Postmeiotic segregation increased 2
CTNNB1 - Catenin beta 1
AXIN1 - Axin 1
AXIN2 - Axin 2
EpCAM - Epithelial cell adhesion molecule
MAP - MUTYH-associated polyposis
PJS - Peutz-Jeghers syndrome
TGF-β - Transforming growth factor beta
NGS - Next-generation sequencing
FISH - Fluorescent in situ hybridization
CGH - Comparative genomic hybridization
AS-PCR - Allele-specific PCR
ctDNA - Circulating tumor DNA

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

ANALIZA GENETSKIH MUTACIJA TP53, APC, KRAS I MMR KOD KOLOREKTALNOG KARCINOMA: PREGLED LITERATURE

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Uvod: Kolorektalni karcinom (KRK) predstavlja jedan od najčešćih malignih tumora sa značajnim zdravstvenim posledicama širom sveta. Genetske mutacije u genima, kao što su TP53, APC, KRAS i MMR geni, igraju značajnu ulogu u razvoju i progresiji ovog karcinoma. U ovom preglednom radu, analizirane su dosadašnje spoznaje o uticaju ovih mutacija na karcinogenezu kolorektalnog karcinoma-a, koristeći dostupnu literaturu.

Cilj: Pružiti uvid u ulogu genetskih mutacija u TP53, APC, KRAS i MMR genima u razvoju kolorektalnog karcinoma i razmotriti njihov uticaj na dijagnostiku i lečenje bolesti.

Materijal i metode: U ovom pregledu analizirani su relevantni istraživački članci i izveštaji iz baze podataka PubMed, Google Scholar i drugih akademskih izvora. Fokus je bio stavljen na studije koje istražuju genetske mutacije, njihovu prevalenciju i ulogu u patogenezi KRK-a.

Rezultati: Mutacije u TP53 genu, koje su prisutne u više od 50% slučajeva KRK-a, ključne su za maligne transformacije ćelija. KRAS mutacije, prisutne u oko 50% slučajeva, dovode do abnormalne signalizacije koja doprinosi nekontroliranom rastu ćelija. APC mutacije povezane su sa naslednom predispozicijom za KRK, dok MMR geni, kao što su MLH1 i MSH2, igraju ključnu ulogu u popravku DNK i povezani su sa sindromom nasledne nepolipozne kolorektalne karcinomatoze.

Zaključak: Genetske mutacije u TP53, APC, KRAS i MMR genima igraju značajnu ulogu u razvoju kolorektalnog karcinoma. Razumevanje ovih mutacija može unaprediti strategije za dijagnozu i lečenje bolesti, kao i pružiti smernice za buduća istraživanja u ovom području.

***Ključne re*čи**: Kolorektalni tumori, Karcinogeneza, Mutacija, Geni, Tumorski supresorski geni,

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