

Review Article

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The role of mutations in the MUTYH gene in the development of colorectal cancer

Mutations in the MUTYH gene, which encodes a DNA glycosylase, are associated with an increased risk of colorectal cancer (CRC), particularly in individuals with hereditary MUTYH-associated polyposis (MAP). MUTYH is an essential component of the base excision repair (BER) pathway, where it removes adenine residues that are mispaired with 8-oxoguanine (8-oxoG), a major product of oxidative DNA damage. Loss of MUTYH function caused by pathogenic variants promotes the accumulation of oxidative DNA damage-associated mutations, including G:C→T:A transversions, thereby contributing to genomic instability and colorectal tumorigenesis. This review examines the pathogenic mechanisms underlying MAP and its characteristic phenotypic features. Structural and functional studies indicate that many pathogenic MUTYH variants result in reduced adenine DNA glycosylase activity, leading to impaired base excision repair. Potential therapeutic strategies aimed at restoring or compensating for defective MUTYH function are being investigated, including approaches based on synthetic lethality. Increasing attention is also being paid to molecular genetic testing for biallelic pathogenic variants in the MUTYH gene, particularly in individuals with clinical or family histories suggestive of hereditary colorectal cancer or polyposis. Identification of such variants may enable more precise risk assessment and facilitate personalized surveillance and preventive management. Overall, advances in understanding the role of MUTYH in genome maintenance have provided important insights into the pathogenesis of MAP and created opportunities for improving the diagnosis, risk stratification, and management of colorectal cancer.

Keywords: base excision repair, adenine DNA glycosylase, DNA repair, MUTYH, colorectal cancer.

Introduction

Colorectal cancer (CRC) is one of the most common types of cancer worldwide. It is the third most common cause of illness and the second most common cause of cancer-related death. Its development reflects a multifactorial process driven by the interplay of genetic predisposition, epigenetic alterations, and environmental influences. Although most CRC cases are sporadic, approximately 5–10 % are associated with inherited genetic defects. Among the best-characterized hereditary CRC syndromes are Lynch syndrome, caused by deficiencies in the DNA mismatch repair (MMR) system, and familial adenomatous polyposis (FAP), which arises from pathogenic mutations in the APC gene [1, 2].

Nevertheless, a subset of patients presenting with multiple colorectal polyps or early-onset CRC lacks detectable mutations in either APC or MMR genes. The identification of biallelic mutations in MUTYH led to the recognition of a distinct hereditary condition known as MUTYH-associated polyposis (MAP) [3, 4]. The MUTYH gene encodes a DNA glycosylase that functions within the base excision repair (BER) pathway, which is essential for protecting the genome from oxidative DNA damage, particularly lesions involving 8-oxoguanine (8-oxoG) [5, 6].

A unique feature of MUTYH is its role in preventing G: C→T: A transversion mutations by excising adenines mispaired with 8-oxoG during DNA replication. When MUTYH activity is compromised, these mutagenic lesions persist, leading to the accumulation of somatic mutations in critical cancer-related genes, most notably APC, a hallmark molecular feature of MAP-associated tumors [4, 7].

This review summarizes current knowledge on the biological function of MUTYH in DNA repair, the molecular basis and clinical characteristics of MAP, and the consequences of MUTYH dysfunction for ge-

nome stability. In addition, it discusses the diagnostic relevance of MUTYH mutations and emerging perspectives for targeted and preventive therapeutic strategies.

Base Excision Repair and the Role of MUTYH

Base excision repair (BER) represents the principal DNA repair pathway responsible for the removal of non-bulky base lesions arising from oxidation, deamination, and alkylation. This pathway is initiated by DNA glycosylases, which recognize damaged bases and cleave the N-glycosidic bond between the base and the deoxyribose, generating an apurinic/aprimidinic (AP) site. Some glycosylases additionally possess β -lyase activity, allowing cleavage of the DNA backbone at the 3' side of the AP site and thereby influencing the subsequent steps of repair [8, 9].

Among BER glycosylases, MUTYH occupies a unique position. Unlike most glycosylases, which directly excise damaged bases, MUTYH removes undamaged adenines mispaired with oxidized guanine (8-oxo-7,8-dihydroguanine, 8-oxoG) during DNA replication. This activity prevents the fixation of G: C $\rightarrow$ T: A transversion mutations, one of the most frequent mutational outcomes of oxidative stress. Loss of MUTYH function leads to the accumulation of somatic mutations in cancer-related genes, including APC, and underlies the development of MUTYH-associated polyposis (MAP). MUTYH operates in concert with other repair enzymes: OGG1 excises 8-oxoG opposite cytosine, whereas MTH1 sanitizes the nucleotide pool by hydrolyzing oxidized dNTPs. Together, these enzymes form a coordinated, multi-layered defense against 8-oxoG-induced mutagenesis [10, 11].

BER proceeds through two main subpathways: single-nucleotide BER (SN-BER) and long-patch BER (LP-BER). In SN-BER, only the damaged nucleotide is replaced, whereas LP-BER involves the removal and resynthesis of a short DNA segment comprising 2–10 nucleotides. When the initiating glycosylase possesses AP-lyase activity, the repair process proceeds through strand incision followed by gap filling by DNA polymerase β and ligation mediated by XRCC1 and DNA ligase III. In contrast, glycosylases lacking lyase activity rely on APE1-mediated incision, followed by strand displacement synthesis involving PCNA, DNA polymerases δ/ϵ , FEN1, and DNA ligase I. The selection of either pathway depends on the nature of the lesion and the biochemical properties of the initiating enzyme, ensuring flexibility and accuracy of repair under conditions of oxidative stress or during replication [8, 12, 13] (Fig. 1).

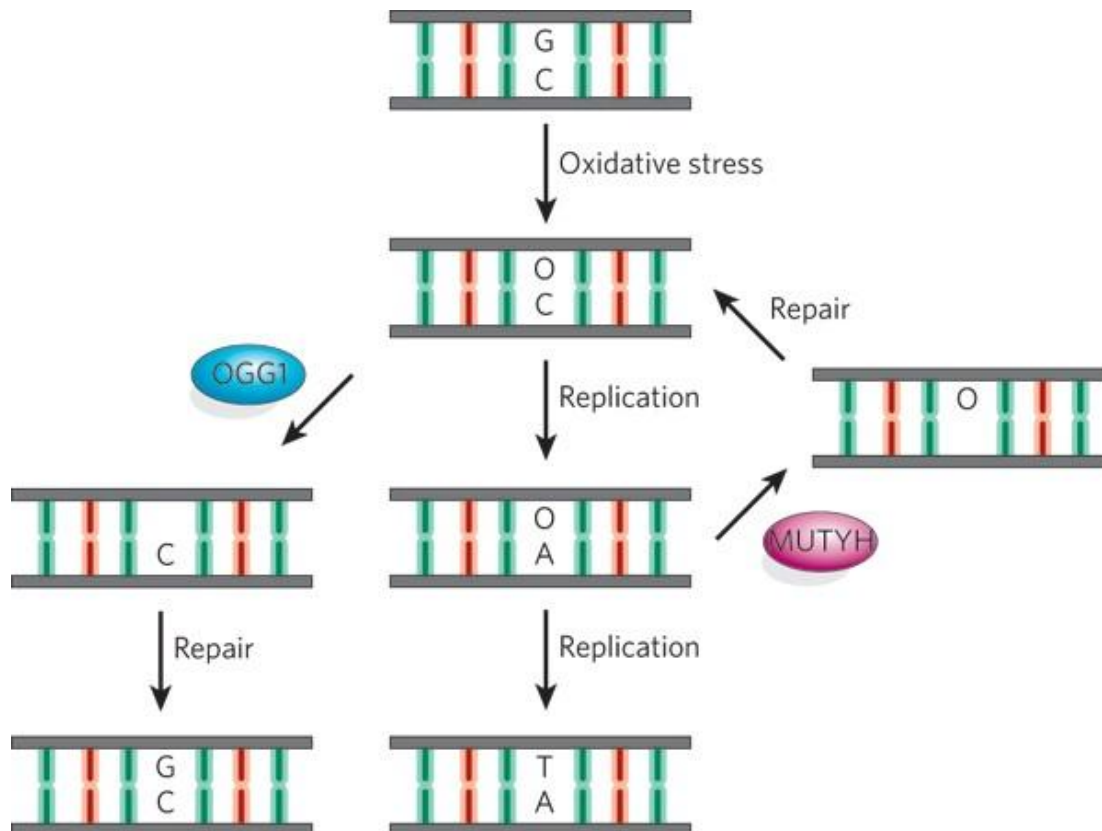


Figure 1. Short-patch base excision repair (BER) pathway for 8-oxoG lesions [8]

Oxidative damage to guanine resulting in 8-oxoG formation is particularly mutagenic. If unrepaired, 8-oxoG can mispair with adenine during DNA synthesis, leading to G: C→T: A transversions. Such mutations are frequently detected in early stages of colorectal carcinogenesis [9]. Consistent with this observation, MUTYH deficiency is associated with a characteristic mutational signature dominated by G: C→T: A substitutions, which represents a molecular hallmark of MAP [11, 14].

Human MUTYH consists of an N-terminal catalytic domain responsible for adenine excision and a C-terminal domain involved in recognition of 8-oxoG. These structural features are conserved in the bacterial homolog MutY, highlighting the evolutionary preservation of MUTYH function [11]. A defining structural element of MUTYH is a highly conserved [4Fe–4S] cluster located within the C-terminal domain. This metallocluster, characteristic of the helix–hairpin–helix (HhH) DNA glycosylase superfamily, plays a critical role in maintaining protein stability and facilitating substrate recognition [15].

Biochemical and structural studies indicate that the [4Fe–4S] cluster does not participate directly in redox catalysis but instead contributes to DNA binding and lesion detection. By stabilizing the HhH-GPD motif, the cluster enables proper alignment of MUTYH with the DNA duplex and supports the base-flipping mechanism required for identifying adenines mispaired with 8-oxoG. Disruption of the Fe–S cluster, whether through mutagenesis or impaired metal coordination, markedly reduces DNA binding affinity and glycosylase activity [16, 17]. Crystallographic analyses further demonstrate that the cluster is positioned at the protein–DNA interface, suggesting a role in recognizing the distinctive structural and electronic properties of 8-oxoG [15].

The human MUTYH gene is located on chromosome 1p34.1, spans about 11.2 kb, and contains 16 exons. It partially overlaps with the TOE1 gene, suggesting a complex regulatory framework at this locus. Multiple alternative promoters produce different transcription variants that encode isoforms with distinct subcellular localizations. Nuclear isoforms mainly repair genomic DNA, while the mitochondrial isoform protects mitochondrial DNA from oxidative damage. This targeting helps MUTYH maintain genomic integrity in different cellular compartments (Fig. 2) [18].

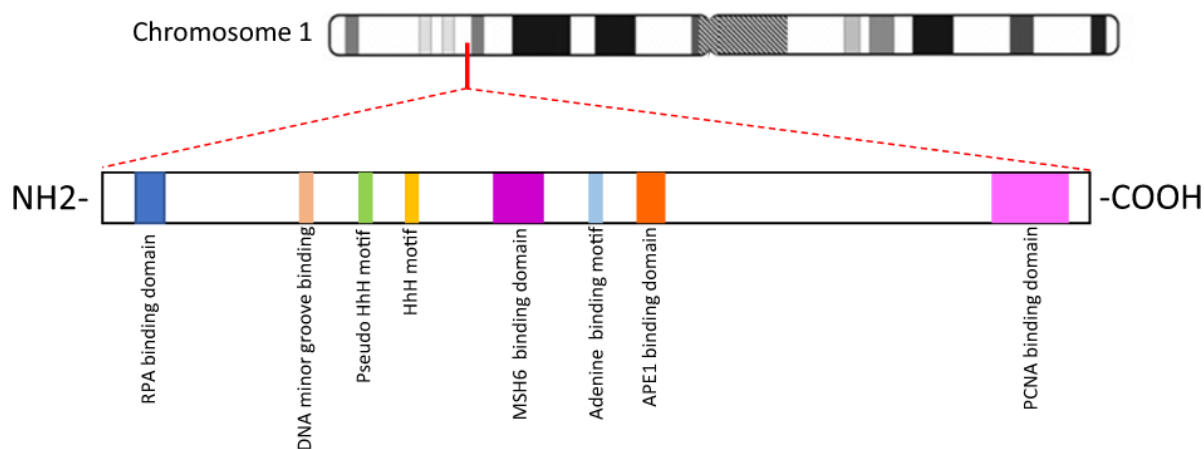


Figure 2: The chromosomal localization and functional domains of MUTYH [18]

Recent studies have improved the understanding of MUTYH's functions by showing its interaction with mismatch repair proteins, especially MSH6, which helps detect DNA damage and form the repair complex. Post-translational modifications, such as phosphorylation and ubiquitination, play a crucial role in controlling the stability, subcellular localization, and catalytic activity of MUTYH. These regulatory mechanisms provide fine control over BER and help prevent excessive or aberrant base excision [8, 18, 19].

Importantly, MUTYH acts as a mismatch-specific rather than a damage-specific glycosylase. By excising adenine from 8-oxoG: A mismatches, MUTYH creates a substrate for correct cytosine incorporation, thereby allowing OGG1 a second opportunity to remove the oxidized guanine. The efficiency of this repair process depends on DNA structure, chromatin context, and replication status, underscoring the adaptive role of MUTYH in proliferating cells (Tab. 1) [20–24].

Table 1

Functional roles of MUTYH in genome maintenance and disease prevention

Role of MUTYH	Molecular mechanism	Biological significance	Clinical implications	Key references
Removal of mispaired adenine opposite 8-oxoG	Hydrolysis of N-glycosidic bond; recognition of A:8-oxoG via HhH-GPD domain	Prevents G: C→T: A transversions; maintains replication fidelity	Loss of function → MAP phenotype; accumulation of APC mutations	[8, 10]
Cooperation with OGG1 and MTH1 (8-oxoG defense axis)	Acts downstream of OGG1 and in coordination with MTH1 to counteract oxidative lesions during and after replication	Provides multi-layered protection against oxidative mutagenesis	Disruption of this axis increases oxidative mutational burden; the strongest clinical evidence for CRC is associated with biallelic MUTYH deficiency	[8, 9]
Crosstalk with mismatch repair (MSH6)	Physical and functional interaction with MSH6 enhances mismatch recognition and repair complex assembly	Improves post-replicative repair efficiency	May contribute to Lynch-like molecular features in a subset of MUTYH-deficient tumors	[23, 24]
Coordination with the DNA replication machinery	Interaction with PCNA localizes MUTYH to replication forks	Enables rapid correction of mismatches arising during DNA synthesis	Impaired interaction increases mutational load and cancer susceptibility	[15, 19]
Function of the [4Fe-4S] cluster	Stabilizes DNA-binding conformation and supports allosteric control	Ensures accurate lesion recognition and structural integrity of the enzyme	Variants destabilizing the Fe-S cluster are associated with severe loss-of-function phenotypes	[15]
Regulation by post-translational modifications	Phosphorylation and ubiquitination modulate stability, localization, and activity	Fine-tunes BER according to cell cycle and stress conditions	Dysregulation may contribute to cancer susceptibility	[23]
Tumor suppression beyond the colon	Prevention of oxidative mutagenesis in multiple tissues	Extends protective role beyond colorectal epithelium	Supports the concept of a broader “MUTYH-associated tumor spectrum”	[4]

Discovering and expanding the role of MUTYH in cancer susceptibility

The discovery of MUTYH-associated polyposis (MAP) was a watershed moment in our understanding of hereditary colorectal cancer syndromes (CRC). Before this, the majority of hereditary CRC cases were linked to dominant mutations in the APC gene (familial adenomatous polyposis) or the mismatch repair (MMR) genes (Lynch syndrome). However, in certain cases, mutations in these canonical genes were not related with numerous adenomas or early development of prostate cancer.

In 2002, a British family was identified as having multiple occurrences of colon cancer and a high frequency of G: C to T: A transversions in the APC gene, indicating a failure to repair oxidative DNA damage. Sequencing showed harmful mutations in the MUTYH (Y179C and G396D) gene implicated in basic excision repair (BER), resulting in the discovery of a novel condition, MAP (MUTYH-associated polyposis) [25].

A comprehensive case-control research found that carriers with biallelic MUTYH mutations had an 18-fold increased risk of cancer, confirming the significance of this finding [23]. Interestingly, heterozygous carriers had a minor but statistically significant increase in cancer risk (risk factor = 1.5), implying MUTYH plays a broader role in cancer propensity [24].

MUTYH was initially linked to colorectal tumor growth, but new research suggests that it plays a larger biological role in preserving genomic stability in many tissues. Its primary role is to remove adenines that are incorrectly linked to 8-oxoguanine, so protecting the genome from oxidative stress-induced mutations. Studies on MUTYH-deficient mice have revealed an increased frequency of spontaneous mutations as well as an increase in the number of tumors not only in the gastrointestinal tract but also in the lungs, liver, and lym-

phatic system. When subjected to oxidative stressors like potassium bromate or ionizing radiation, these mice develop more varied and severe tumors than wild-type controls.

At the molecular level, MUTYH is involved in transcriptional repair and interacts with mismatch repair proteins such as MSH6, implying a function in coordinating numerous genome maintenance mechanisms [22]. Furthermore, posttranslational changes including phosphorylation, ubiquitination, and interaction with replication-related proteins like PCNA, influence MUTYH function and cellular location [21].

Furthermore, discoveries have highlighted the epigenetic control of MUTYH. For example, Alfeghaly et al. (2019) discovered that the long non-coding RNA ANRIL controls the expression of DNA repair genes, including MUTYH, implying that tissue-specific expression and cancer risk may be generated by RNA regulation [23].

Clinically, MUTYH allelic mutations have been observed in tumors other than the colon, including ovarian, endometrial, and probably kidney cancers; the degree and causation of these connections are currently being investigated. As genome-wide association studies (GWAS) and genetic screening panels for many malignancies become increasingly popular, the whole spectrum of MUTYH tumor suppressor activity is expected to broaden.

As Curia, Catalano, and Aceto et al. point out, MUTYH is increasingly recognized as a multifunctional genome caregiver rather than a CRC-specific tumor suppressor. Its involvement in oxidative DNA repair, interaction with essential repair proteins, stress signaling, and vulnerability to epigenetic modification highlight its importance in cellular homeostasis and cancer prevention [26].

The clinical implications of MUTYH mutations in colorectal cancer

The discovery of MUTYH-associated polyposis (MAP) had far-reaching clinical implications, especially in the field of genetic counseling, diagnosis, and treatment of colorectal cancer (CRC). As an autosomal recessive disease, MAP is a problem distinct from dominantly inherited syndromes such as familial adenomatous polyposis (FAP) and Lynch syndrome. For the disease to develop, individuals must inherit two harmful mutations, one from each parent, while heterozygous (monoallelic) carriers are usually asymptomatic. This complicates the risk assessment based solely on family history and highlights the need for molecular diagnostics [26, 27].

Genetic testing for MUTYH mutations is currently standard practice in individuals with multiple colorectal adenomas (usually 10–100), especially when no pathogenic variants have been identified in the APC gene [29]. In European populations, the most common mutational variants are Y165C and G382D, which are usually included in targeted testing programs. Next-generation sequencing (NGS) has expanded the possibilities of detecting rare and population-specific mutations [30].

After the diagnosis of MAP, clinical guidance is based on enhanced surveillance. Colonoscopy should begin in the third decade of life with a follow-up interval of 1–2 years, depending on the prevalence of the adenoma and histological examination. Preventive colectomy may be recommended for patients with a high prevalence of adenoma or dysplasia, similar to treatment for advanced FAP [31]. Screening of the upper gastrointestinal tract, such as esophagogastroduodenoscopy, is also recommended due to the increased risk of developing duodenal and gastric polyps [32].

Comprehensive testing of family members is required. Relatives of those affected should undergo genetic counseling and, if necessary, mutation testing. Early detection of carriers of biallelic genes allows timely implementation of surveillance strategies, potentially preventing CRC [33]. Although MAP does not develop in monoallelic carriers, some studies suggest a slightly increased risk of CRC, especially in the presence of environmental or genetic cofactors.

MUTYH is increasingly being included in multigenic panels to determine cancer predisposition, which is beneficial for patients with atypical phenotypes or lack of family history. However, broader testing increases the likelihood of identifying variants with uncertain significance (VUS), which complicates clinical interpretation, especially in individuals without overt polyposis [34].

Emerging data on the epigenetic regulation of MUTYH may suggest new diagnostic and prognostic approaches. Long non-coding RNAs (lncRNAs) such as ANRIL have been shown to modulate the expression of DNA repair genes, including MUTYH, suggesting that transcriptomic profiling can improve risk stratification [20].

Thus, the identification of MUTYH as the main gene in hereditary CRC has had a profound impact on clinical practice, providing more accurate risk assessment, personalized follow-up, and integration of

MUTYH testing into complex cancer genetics. Recent advances in genomics and transcriptomics are expected to further improve clinical care for MAP and related conditions [28].

Major studies conducted over the past decade confirm the multifaceted role of MUTYH in maintaining genomic integrity and preventing hereditary cancers, particularly colorectal cancer. Biallelic mutations lead to MUTYH dysfunction, resulting in the formation of MAP, characterized by numerous adenomatous polyps and a significantly increased risk of CRC. Epidemiological data indicate an 18-fold higher risk in biallelic carriers, while heterozygous carriers show a moderately increased risk.

MUTYH is necessary for the basic excision repair (BER) pathway, removing adenines improperly incorporated into 8-oxoG, and supplementing the activity of OGG1 and MTH1 to protect against mutagenesis caused by reactive oxygen species. Recent studies have highlighted its interaction with other repair pathways, including mismatch repair (MMR), and the effect of posttranslational modifications on MUTYH activity and localization [35].

Conclusion

In conclusion, identifying MUTYH-associated polyposis (MAP) has improved our understanding of hereditary colorectal cancer. It emphasizes the key role of base excision repair in preventing tumor formation. The MUTYH protein ensures the maintenance of genomic stability by removing adenine mistakenly paired with oxidized guanine, thereby preventing the accumulation of mutations. This mechanism is an important component of the dynamic balance between DNA damage and repair. The functions of MUTYH are not limited to colorectal tissue but also include participation in the cellular response to oxidative stress and epigenetic regulatory processes, indicating its broader systemic significance. It has been shown that molecular genetic testing for MUTYH mutations improves the accuracy of individual risk assessment and clinical management in hereditary colorectal cancer. However, challenges persist in the interpretation of variants and the assessment of cancer risk in cases not limited to the colon. It is suggested that future research into the regulatory mechanisms of MUTYH may result in the identification of novel biomarkers and targeted therapeutic strategies. Overall, MUTYH demonstrates the capacity for molecular insights to be translated into enhanced clinical practice for hereditary cancer syndromes.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

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MUTYH геніндегі мутацияның колоректалды кәтерлі ісіктің дамуындағы рөлі

MUTYH геніндегі мутациялар ДНК-гликозилазаны кодтай отырып, колоректалды кәтерлі ісіктің (КРКІ) дамуында, әсіресе MUTYH-пен байланысты полипоз (МАР) жағдайларында маңызды рөл атқарады. Бұл фермент ДНК-ның негіздерін эксцизиялық репарациялау (BER) үдерісінің негізгі компоненті және ДНК-ның тотығу зақымдануының өнімі болып саналатын 8-оксогуанинмен (8-oxoG) қате жұптасқан адениндерді жоюға жауап береді. MUTYH функциясының патогенді мутациялар салдарынан бұзылуы G: C→T: A типті трансверсиялардың жинақталуына әкеліп, геномдық тұрақсыздықтың күшеюіне және тоқ ішек эпителий жасушаларының кәтерлі трансформациясына себеп болады. Бұл шолуда MUTYH дисфункциясының колоректалды кәтерлі ісіктің дамуымен байланысын дәлелдейтін молекулалық, функционалдық және клиникаға дейінгі деректер жинақталған. МАР синдромының патогенетикалық механизмдері мен фенотиптік ерекшеліктері талқыланып, MUTYH-тың әртүрлі нұсқаларында ферментативтік белсенділіктің төмендейтінін көрсететін құрылымдық талдаулардың нәтижелері ұсынылады. Қазіргі уақытта MUTYH функциясын қалпына келтіруге бағытталған терапиялық стратегиялар, соның ішінде гендік терапия, фармакологиялық модуляция және синтетикалық өлім қағидаттарына негізделген тәсілдер зерттелуде. Отбасылық анамнезінде колоректалды кәтерлі ісігі бар адамдарда MUTYH генінің биаллельді мутацияларын ерте молекулалық скринингтен өткізуге ерекше назар аударылады, өйткені бұл деректер алдын алу мен емдеудің дербестендірілген тәсілдерін қалыптастыру үшін маңызды негіз бола алады. MUTYH-тың геном тұтастығын сақтаудағы рөлін терең түсіну колоректалды кәтерлі ісікті диагностикалау, қауіп-кәтерді бағалау және таргеттік терапияны дамыту үшін жаңа мүмкіндіктер ашады.

Кілт сөздер: негіздерді эксцизиялық репарациялау, аденин-ДНК-гликозилаза, ДНК репарациясы, MUTYH, колоректалды кәтерлі ісік.

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Роль мутации в гене MUTYH в развитии колоректального рака

Мутации в гене MUTYH, который кодирует ДНК-гликозилазу, играют ключевую роль в развитии колоректального рака (КРР), особенно в случаях наследственного полипоза, ассоциированного с MUTYH (МАР). Этот фермент является важной частью процесса репарации оснований (BER), ответственного за удаление аденинов, неправильно связанных с 8-оксогуанином (8-охоG), побочным продуктом окислительного повреждения ДНК. Потеря функции MUTYH из-за вредных мутаций приводит к накоплению трансверсий G:C→T:A, что приводит к нестабильности генома и злокачественной трансформации эпителиальных клеток толстой кишки. В этом обзоре обобщены молекулярные, функциональные и доклинические данные, подтверждающие связь дисфункции MUTYH с развитием КРР. В нем обсуждаются патогенетические механизмы и фенотипические особенности МАР, представлены результаты структурного анализа, показывающие снижение ферментативной активности в различных вариантах MUTYH. В настоящее время изучаются терапевтические стратегии, направленные на восстановление функции MUTYH, включая генную терапию, фармакологическую модуляцию и использование синтетической летальности. Особое внимание уделяется раннему молекулярному скринингу на наличие биаллельных мутаций MUTYH у лиц с семейным анамнезом КРР, поскольку он может служить основой для персонализированных подходов к профилактике и лечению. Понимание роли MUTYH в поддержании целостности генома открывает новые возможности для диагностики, оценки риска и таргетной терапии колоректального рака.

Ключевые слова: удаление основания, аденин-ДНК гликозилаза, репарация ДНК, MUTYH, колоректальный рак.

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