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Review Article

DNA Mismatches Repair Activity in Cells

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Abstract

Mismatch repair (MMR) is a highly conserved biological mechanism that is essential for genomic integrity. MMR is most specific for base-base mismatches and insertion/deletion mispairs that occur during DNA replication and recombination. MMR also slows homeologous recombination and has recently been linked to DNA damage signaling in eukaryotic cells. MutS and MutL from Escherichia coli, as well as their eukaryotic homologs MutS and MutL, are important participants in MMR-associated genome maintenance. Many additional protein components involved in other DNA metabolic pathways, such as PCNA and RPA, are also required for MMR (Therese et al., 2019). MMR mutations are linked to genome-wide instability, propensity to certain forms of cancer, including hereditary non-polyposis colorectal cancer, resistance to some chemotherapeutic drugs, and meiotic and sterility disorders in mammalian systems (Yunusa et al., 2018).

INTRODUCTION

Exogenous chemicals and physical agents (such as benzo[a] pyrene, polychlorinated biphenyls, dioxin, cigarette smoke, asbestos, ultraviolet light, and radon) cause DNA damage in cells over time, as do endogenous reactive metabolites such as reactive oxygen and nitrogen species (ROS and NOS). Errors that occur during normal DNA metabolism or abnormal DNA processing events, such as DNA replication, recombination, and repair, are another form of DNA damage. Nucleotide misincorporation causes DNA base-base mismatches at varying rates during DNA synthesis, depending on a variety of circumstances, including the individual DNA polymerases. In general, replicative DNA polymerases have relatively high replication fidelity, but translesion DNA polymerases have lower replication fidelity because they selectively skip areas of DNA damage. Unrepaired DNA damage has the potential to create mutations in somatic or germline cells, altering cellular phenotype and causing malfunction and illness. Cells have several ways for repairing DNA damage and thereby preventing mutations to prevent such negative consequences and protect the genome's integrity. The important route known as DNA mismatch repair (MMR) is one such mechanism (Celestina et al., 2021).

Certain malignancies develop and advance as a result of a loss of DNA mismatch repair (MMR) function. Assays for DNA MMR activity currently employ cell extracts and are technically difficult and expensive. We present a fast, less labor-intensive approach for quantifying MMR activity in live cells. A G-G or T-G mismatch was inserted into the enhanced green fluorescent protein (EGFP) gene's ATG start codon. Repairing the G-G or T-G mismatch in the heteroduplex plasmid to G-C or T-A, respectively, results in functional EGFP gene production. The heteroduplex plasmid and a homoduplex plasmid were transfected into the same cell line in parallel, and the number of green cells was measured using flow cytometry (Ebeye et al., 2007). The total fluorescence intensity of cells transfected with the heteroduplex construct was divided by the total fluorescence intensity of cells transfected with the homoduplex construct to compute relative EGFP expression. Using this strategy, we evaluated numerous cell lines from both MMR-deficient and MMR-proficient groups, including a colon cancer cell line HCT116 with a faulty hMLH1 gene and a derivative augmented by transient transfection with hMLH1 cDNA. MMR-proficient cells produce considerably more EGFP than MMR-deficient cells, and temporary expression of hMLH1 alone can increase MMR activity in HCT116 cells. This approach might be beneficial for comparing and monitoring MMR activity in live cells under different growth

circumstances (Friday et al., 2015).

MMR repairs DNA mismatches caused by DNA replication, preventing mutations from becoming permanent in dividing cells. MMR deficiencies enhance the rate of spontaneous mutation because MMR minimizes the amount of replication-associated mistakes. MMR inactivation has been linked to hereditary and sporadic human malignancies, and the MMR system is essential for cell cycle arrest and/or programmed cell death in response to certain forms of DNA damage. Thus, MMR participates in the DNA damage response system, which removes severely damaged cells and avoids both mutagenesis and tumorigenesis in the near term (Ogori et al., 2016). Throughout their existence, organisms are subjected to a variety of external and internal stimuli that impact or alter their functioning. Aging has been identified as a significant process that is influenced or affected by various elements. Harman's aging hypothesis proposes that unrepaired oxidative damage to biomolecules induced by free radicals and accumulates during an organism's lifespan may contribute to aging. Based on in vitro and in vivo studies, it has been proven that cellular metabolic processes, such as mitochondrial respiration, produce oxidants that can cause biomolecules to oxidize (Ashaye et al., 2006). Prolonged exposure to pollutants, metals, toxic chemicals, and ionizing radiation can also trigger the degenerative processes that lead to premature aging. When oxidative damage, particularly DNA damage, occurs, it sets off a chain of events that may lead to aging and illness. Cells, on the other hand, have various ways for maintaining the biochemical integrity and stability of DNA. The base excision repair (BER) system is one of them. It is a biological process that repairs damaged bases in the DNA sequence caused by deamination, oxidation, and alkylation. Another DNA repair method that varies from BER is nucleotide excision repair (NER). NER corrects larger amounts of DNA damage by eliminating the strand segment that includes a significant nucleotide lesion, whereas BER fixes individual damaged bases. In cell death, both the BER and NER systems are always active, repairing DNA damage as it is recognized. Other processes, such as the DNA mismatch repair system (MMR), are engaged at particular cellular phases (Banjo et al., 2010).

DNA MMR is an evolutionarily conserved mechanism that corrects base mismatches that occur during DNA replication but are not corrected by the proofreading process. This is performed by the binding of protein heterodimers with the mismatched DNA sequence. Other dimers are subsequently recruited and bind with the DNA to activate repair signals (e.g., MutL or MutH). Specific genes and proteins are activated when the structural integrity of DNA is disturbed. The MutS family of proteins, which is integrated by MSH2, MSH3, and MSH6, is one of these groups. These proteins are extremely conserved across species and were discovered in Escherichia coli; they have gained a lot of interest in recent years because of their link to a number of degenerative and pathologic disorders in humans (Yusuf et al., 2017). MSH proteins detect mistakes in the genome sequence during replication, preventing the damaged strand from being duplicated and mending single strand breaks. In the presence of base mispairing and other mismatches, MSH2 binds to MSH6, creating the MutS heterodimer (MSH2-MSH6), or it binds to MSH3 in the presence of base deletions, making the MutS heterodimer (MSH2-MSH3). After that, the MutS heterodimer attaches to the changed area and recruits MutL family members such MLH1 and PMS2 (as a MutL heterodimer). MLH1 and PMS2 then activate the enzymes required for DNA mismatch repair. Through the activity of DNA polymerase and DNA ligase I, the DNA-MMR complex commences the signalling process to replace the DNA changed region. ATP is required for the recruitment of MMR proteins. Furthermore, the activity of the two MutS dimers at the DNA mismatch site is dependent on interactions with the proliferating cell nuclear antigen (PCNA), a key cofactor in both DNA replication and repair pathways. PCNA interacts with the MutS dimer via its MSH6 domain, and the MutS dimer attaches to it around the MSH3 domain. The purified components of the basic human MMR system were recombinant MutS or MutS, MutL, Exonuclease I (EXOI), PCNA, replication factor C (RFC, which loads PCNA onto DNA), the single-strand binding factor replication protein A (RPA), polymerase, and DNA ligase I. The 5’-to-3’ mismatch-directed strand excision in this system needed just MutS, EXOI, and RPA, but processing substrates with a 3’ nick required MutL, PCNA, and RFC (Ajiboso et al., 2012).

CONCLUSION

Although the majority of studies on MMR insufficiency and chromosomal changes have been linked to carcinogenic processes, there is a strong potential in applying these methods for aging and senescence investigations. MMR impairment research might possibly be utilized to link cancer and aging. Cancer propensity is known to be more common in the elderly when DNA repair is compromised, which coincides with DNA damage accumulation (e.g., MSI) throughout life and may explain the origin of these illnesses as postulated by Harman. Mutations in MMR proteins, on the other hand, have been linked to numerous cancers observed in both geriatric and pediatric individuals, including haematological malignancies, brain tumors, Lynch syndrome, and neurofibromatosis. As a result, it is critical to evaluate whether these malignant diseases are entirely caused by aging or by DNA damage/mutation. Another consideration is the interaction with other protein complexes that may aid in the MMR system. In msh2-knockout mouse embryonic fibroblasts, HEK, and HeLa cell lines, it was recently shown that MSH2 is also in charge of the recruitment of the ATR protein, which, together with the ATM protein, is in charge of the DNA damage response signaling, which is usually linked with cell death through apoptosis. According to the findings, ATR is recruited via two distinct pathways: one mediated by RPA (replication protein A) and sends a signal to the Chk1 protein, while

the other is controlled by MSH2 and is responsible for Chk2 activation. Experiments based on correlations between MMR deficiencies and DNA damage markers in new models, such as bats, could benefit future research by increasing our understanding of MSH2 pathways and revealing new processes that regulate cellular homeostasis by maintaining DNA integrity.

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