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Review

Mechanisms of mutagenesis: DNA replication in the presence of DNA damage

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ABSTRACT

Environmental mutagens cause DNA damage that disturbs replication and produces mutations, leading to cancer and other diseases. We discuss mechanisms of mutagenesis resulting from DNA damage, from the level of DNA replication by a single polymerase to the complex DNA replisome of some typical model organisms (including bacteriophage T7, T4, *Sulfolobus solfataricus, Escherichia coli*, yeast and human). For a single DNA polymerase, DNA damage can affect replication in three major ways: reducing replication fidelity, causing frameshift mutations, and blocking replication. For the DNA replisome, protein interactions and the functions of accessory proteins can yield rather different results even with a single DNA polymerase. The mechanism of mutation during replication performed by the DNA replisome is a long-standing question. Using new methods and techniques, the replisomes of certain organisms and human cell extracts can now be investigated with regard to the bypass of DNA damage. In this review, we consider the molecular mechanism of mutagenesis resulting from DNA damage in replication at the levels of single DNA polymerases and complex DNA replisomes, including translesion DNA synthesis.

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1. Introduction

Large amounts of chemicals are produced in industry, agriculture, and transportation (automobile and truck exhausts). These environmental chemicals can be widespread in air, water, and soil. In 1915, Yamagiwa and Ishikawa [1] reported the formation of tumors in the ears of rabbits after treatment with tars, and in 1933 Cook et al. isolated benzo[*a*]pyrene as a component of coal tar [2]. Many chemicals have now been shown to cause mutations and cancer. Animals have produced tumors after exposure to many environmental mutagens [3]. Human exposure to specific chemical or physical carcinogens also produces characteristic mutational spectra, considered to be highly relevant not only to cancer but also to cardiovascular disease, teratology, and aging [4–6]. Therefore, studies on how chemicals can lead to mutations have received considerable attention.

Beginning in the 1940s, James and Elizabeth Miller showed that these environmental mutagens are converted to reactive products within the body [7]. These compounds react with DNA to form DNA adducts [8,9]. In each human cell, >50,000 DNA damage sites can occur every day [10]. DNA adducts lead to mutations during DNA replication that can further lead to cell death, aging, birth defects, and cancer. Several families of DNA polymerases are involved in DNA synthesis. At least seven families of DNA polymerases have been described, classified based on their sequences and structural similarities: A, B, C, D, X, Y, and reverse transcriptase. Each family has specific functions in DNA polymerization. In general, the A-family and C-family DNA polymerases in prokaryotes, the B-family DNA polymerases in eukaryotes, and the A-family mitochondrial Pol γ in eukaryotes are much faster and accurate (and are termed replicative DNA polymerases) compared with other families of DNA polymerases. The Y-family polymerases carry out translesion DNA synthesis (TLS) and bypass DNA damage in an error-prone or error-free manner. Some TLS DNA polymerases preferentially insert the correct base and do not result in mutation, giving at least 3 outcomes from the process: no mutation, mutation, or cell death.

Generally, the replicative DNA polymerases that perform normal DNA synthesis are replaced by Y-family DNA polymerases when bypassing DNA damage and return back to the replication fork after bypass of the DNA damage [11]. Upon encountering DNA damage, polymerases may misincorporate, be blocked by these adducts, or produce frameshifts, each of which disturbs DNA replication and leads to mutations. The details of how DNA damage disturbs DNA replication will be summarized and analyzed in this review. DNA replication *in vivo* includes both leading- and lagging-strand DNA synthesis, generally not performed by only a single DNA polymerase but by the complex DNA replisome that contains DNA polymerase(s), helicase, primase, single-stranded DNA binding protein, and a number of other accessory proteins [12]. Thus, the DNA replisome plays a critical role in damage bypass, which may not be observed with a single DNA polymerase. The effects of DNA damage on replication by DNA replisomes have not been extensively investigated until recently. It has been accepted that polymerase exchange occurs when a DNA replisome encounters DNA damage. Besides polymerase exchange, other proteins in the replisome may also be involved in the bypass of DNA damage. In this review, we summarize and analyze current studies of the effects of DNA damage on replication by the DNA replisome of *Escherichia coli* and bacteriophages T4 and T7.

In addition to the bypass of DNA damage by DNA polymerases, other proteins in the DNA replisome are also involved in dealing with DNA damage. For instance, the *E. coli* DNA repair helicase $UvrA_2B$ protein complex allows limited ATP-dependent scanning of DNA to detect damaged bases in UV-induced lesions, and the UvrD helicase (helicase II) in *E. coli* nucleotide excision repair (NER) excises damage-containing oligonucleotides [13]. Semi-replicative simian virus 40 (large T antigen) DNA helicases are able to bypass a bulky adduct on the translocated strand [14], bringing a new understanding about the interaction between enzymes and DNA damage.

Overall, DNA damage has a wide range of effects on DNA replication and its related processes. In this review, we will address how DNA damage leads to mistakes in DNA replication from the viewpoint of an individual DNA polymerase (from bacteriophage T7, *S. solfataricus, E. coli*, yeast or human) and the DNA replisome (of *E. coli*, bacteriophage T7 or T4). The studies about single DNA polymerases were mainly contributed by Gugenerich's lab. Because the human DNA replisome is far more difficult to study, the human DNA replication complex will be discussed only briefly at the end of this review. Mutations arising from DNA repair are not included in this review. DNA damage has a wider effect on living systems beyond DNA replication and the DNA polymerase and DNA replisome, scientific areas which should also be further explored. We have selected some typical DNA polymerases and types of DNA damage to describe mechanisms of mutation in the presence of DNA damage.

2. Environmental mutagens cause DNA damage

2.1. Environmental mutagens cause cancer

Environmental mutagens damage the genome by forming DNA adducts through different chemical reactions [15], including alkylation (which may involve cross-linking), oxidation, deamination, coordination, photo-addition, and hydrolysis (Table 1). Alkylating agents produce N^2-alkyl-2′-deoxyguanosine (N^2-alkylG), O^6-alkylguanine (O^6-alkylG), polycyclic aromatic hydrocarbon DNA adducts (PAH-DNA), and etheno (ε) DNA adducts. Bis-