How do Errors caused by DNA Polymerase in replication affect human health and contribute to the development of Cancer

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1 Abstract

Many factors lead to errors in DNA polymerase function that cause many mutations during DNA replication, which negatively affects human health, and some people die due to their impacts. Moreover, there is a gap in identification at this point. So, the process of DNA replication and the specific errors usually caused by factors that affect DNA polymerase during replication have been explained solely with the negative impacts affecting human health that each type of these errors causes. In addition, the effect of these errors on developing cancer has been mentioned with the lifestyle, nutritional habits, and improvements that can be done to decrease the rate of the explained errors which are from reasons of developing cancer and some other mentioned diseases. Moreover, the relationship between climate change and the increase in these errors was discussed in addition to some steps to follow to reduce mutations in DNA. Furthermore, the difficulties that governments and business owners face in making major changes to decrease the rate of these mutations were also mentioned. Finally, this literature review aims to help reduce the rate of these mutations, the cancer rate, and people's awareness about this topic.

2 Introduction

What do we know about errors in DNA replication? What are the causes and impacts of these errors, and how to avoid them?

Firstly, during DNA replication, there is an enzyme called DNA polymerase, which is responsible for many things. First, this enzyme reads the template strand of the molecule of DNA after the unwinding and uses it as a guide to complete it with the second strand. Then, the DNA polymerase uses the information from the template strand to add nucleotides to the second strand in a sequence according to the template strand. The next step is proofreading, where the enzyme checks the newly formed strand for any errors in base pairing and corrects it by removing and adding a new one. At last, The DNA polymerase continues to add nucleotides to the new strand until replication is completed. Moreover, during this trip, many errors

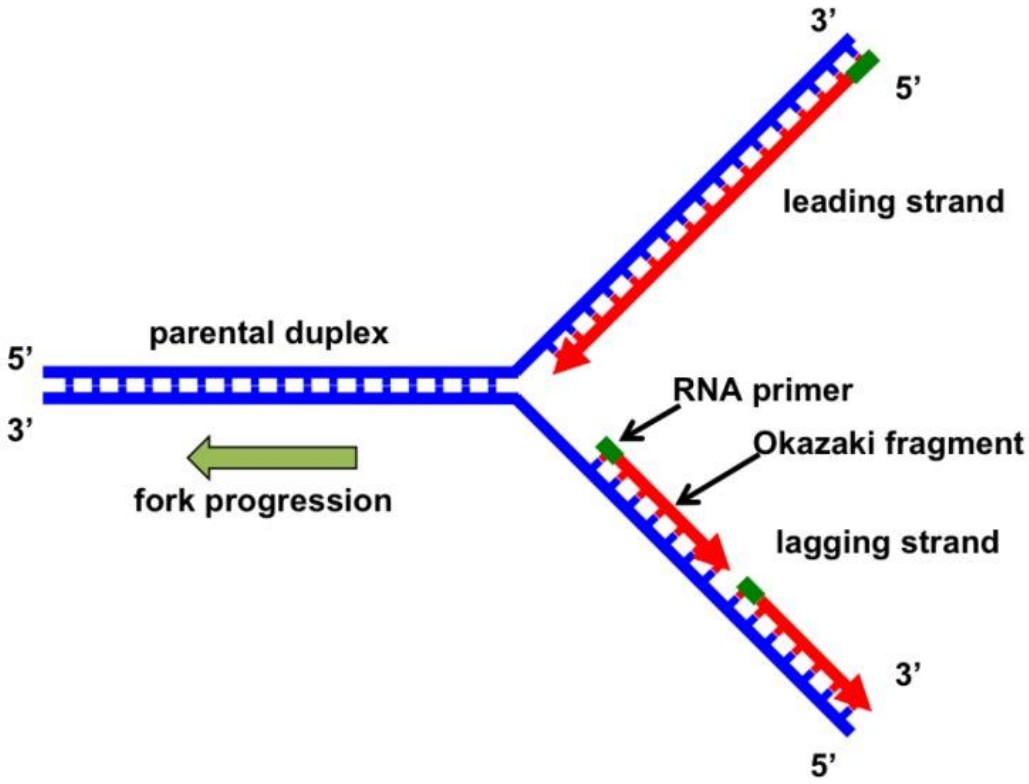
can occur in base pairs due to many factors with a rate ranging from 10^{-9} to 10^{-10} per each replication cycle, contributing to the development of Cancer and some other diseases[1] . These errors will be explained, and how to decrease the percentage of these errors.

DNA polymerases are divided into two groups: replicative and non-replicative. This paper discusses errors in replicative DNA polymerase that cause mutations and contribute to cancer development, with the lifestyle and strategies to follow to decrease these errors and mutations. If these recommendations are followed, then people will know why these errors occur, decrease the rates of mutations and Cancer, and give solutions to decrease the percentage of these errors.

3 Literature review

3.1 DNA replication

DNA replication is a process where DNA duplicates. Firstly, the DNA double strands are unzipped by an enzyme called “helicase.” This enzyme breaks the hydrogen bonds between the nucleotides; after that, the



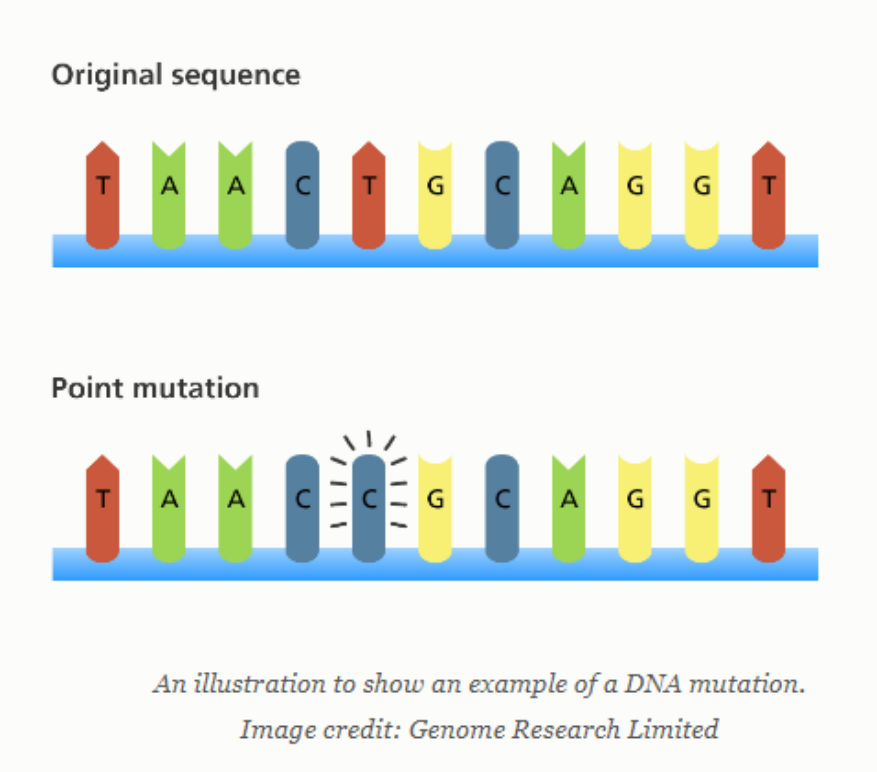
separation of the double helix creates a “Y” shape called “Fork,” as shown in Figure (1).

Figure (1)

Moreover, the two separated strands act as a template for the new strands. One strand is in the 3’ to 5’ direction, which is called the leading strand; the other strand is in the 5’ to 3’ direction, which is called the lagging strand. After that, a small piece of RNA called “Primer” plays the role of the starting point for DNA synthesis. Next, there is an enzyme called “DNA polymerase” that moves along the leading strands, adding new complementary nucleotides in the 5’ to 3’ direction [2]. Lastly, “DNA ligase” joins the gaps in the phosphodiester backbone in the new strand due to the movement of DNA polymerase in 5’ to 3’direction [3].

3.2 Errors in DNA replication caused by DNA polymerase:

Firstly, Mutation is a permanent change in the sequence of DNA that may create a new allele of a gene. Moreover, there are many mutations that can arise during replication due to some errors which are



An illustration to show an example of a DNA mutation.
Image credit: Genome Research Limited

related to many things such as our diet, harmful chemicals, and exposure to large dosages of radiation. Furthermore, there is a type of mutation that may occur during DNA replication: point mutations. This type of mutation is associated with the exchange of a nucleotide with another nucleotide, as shown in Figure (2). In addition, this type

Figure (2)

of Mutation can alter proteins' composition by forming an amino acid that codes for different protein or inhibits its function. Moreover, many diseases can occur due to these mutations, For example, Cystic fibrosis, Sickle-cell anemia, and Tay Sachs [4].

Second, DNA polymerase can mismatch and put the wrong nucleotide during DNA replication. However, a mechanism called “proofreading” is responsible for correcting these errors, but it does not always work. Many diseases are caused by this type of error, like human neuromuscular and ophthalmologic diseases [5].

Third, Frameshift mutations, this type of mutations occur by the deletion or addition of nucleotide bases that are not from the multiples of three. Moreover, there is something called codon, which is made up of three nucleotides and is translated into amino acids, which are the building blocks of proteins. In this type of mutation, there are wrong-coded amino acids, which will alter the formation of proteins. These mutations can have many impacts, like genetic disorders, loss of protein function, altered gene regulation, and impaired enzyme activity [6].

The last type, repeat expansion errors, is a mutation associated with the expansion of repetitive DNA sequences. This type of mutation occurs when these sequences have abnormal growth in length during DNA replication, such as trinucleotide repeat expansion, which is a repeat of a sequence of three nucleotides [7]. In addition, it may cause the resulting proteins to not function properly [8] and cause many

neuromuscular diseases such as myotonic dystrophy and Huntington's disease [9].

3.3 Errors in DNA polymerase during replication and the development of Cancer

Cancer is a disease caused by abnormal cell division. Moreover, abnormal cell division can occur due to many reasons. First, mutations that activate proto-oncogenes, which play an essential role in cell growth, division, and differentiation, through alterations or errors in their encoded proteins and make them become oncogenes (a mutated form of the gene) is due to point mutations, insertion, and deletion of nucleotide bases [10]. Second, the inactivation of tumor suppressor genes, which are genes that inhibit the development of tumor and cell proliferation, that is caused by disrupting the function of the encoded proteins by the gene due to deletions or point mutations [11]. Furthermore, Factors to reduce these errors are discussed as follows.

3.4 Lifestyle and environmental factors that contribute to the development of cancer, reduce human health and cause many diseases and how to reduce their effects.

Nutrients in our food can reduce DNA mutations. Following healthy and nutritional-rich diets such as those which are rich in crucial antioxidative micronutrients such as selenium, zinc, vitamin C, and vitamin E can increase DNA synthesis stability and decrease mutations [12]. On the other hand, following unhealthy and nutritional poor diets can have the opposite effect. For example, B-vitamin deficiency weakens DNA stability [13].

Exposure to harmful chemicals and radiation can alter the chemical behavior of the DNA and cause DNA to mutate. For example, harmful chemicals like those found in plastics or cigarettes can cause alterations in the chemical behavior of the DNA bases, which can lead to substituting one DNA base with another [14]. In addition, exposure to large dosages

of harmful radiation can lead to mutations in DNA. For instance, exposure to a large dosage of UV radiation breaks DNA strands and lead to some alterations such as thymine dimers [15].

Education and awareness are also related to minimizing the mutations in DNA. Increasing the education quality and public awareness will lead to a depletion in the mutation rates by knowing the causes and consequences of these mutations. To sum up, the way to reduce genetic alterations and errors is by following a nutritional diet, being away from mutagens, following a healthy lifestyle, and increasing the awareness with these mutations.

4 Discussion

People should be aware of the reasons for cancer and prevent it. According to the World Health Organization, cancer rates are continuously growing globally, and 30% to 50% of cancer deaths can be avoided by following a few things that people must be aware of. For example, maintain or avoid tobacco use, get proper medical care, have safe sex, reduce alcohol use, have a healthy weight, avoid air pollution, and exercise regularly. Moreover, governments and big companies should contribute to people's awareness by making campaigns or programs to increase awareness for the reasons of cancer, which is a gap in many areas worldwide.

All mentioned sources have agreed about the types of errors in DNA during replication and how it risks people worldwide. According to the American Association for Cancer Research, climate change negatively impacts human health. Specifically, causing mutations due to the environmental effects of carbon emissions and climate change could lead

to an increase in the risks of cancer. Efforts to decrease deforestation, enhance vehicle emissions standards, and invest in renewable energy can cause climate change to decline.

Working on reducing mutagens is not very quick due to many reasons. Policies or laws that limit or control the exposure to mutagens often involve land and economic loss. In addition, many mutagens have long-term effects on human health, which may take decades to observe. Moreover, researching and developing strategies to deal with mutagens by studying and observing them often takes much time. Lastly, introducing changes to practices, industries, and consumer behavior to reduce mutagens faces many difficulties from the owners of the businesses.

5 Conclusion

Recent research and academic books have identified what DNA replication is, the role of DNA polymerase during DNA replication, specific errors that can be caused by DNA polymerase in DNA replication due to many factors, the dangers of these errors on human health, and how to decrease its rate by following some strategies. However, there is a gap in knowledge between people about the impacts of the mentioned errors on their health and the lifestyle habits to decrease the rate of these errors. So, this literature review aims to make people aware of daily things that might cause mutations, negatively affect their health, and give rise to various diseases such as cancer. Furthermore, it aims to represent ways to decrease the percentage of these mutations. In addition to discussing the difficulties that face governments and business owners taking steps towards limiting factors that cause these alterations to increase.

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