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Perspective

Spontaneous Mutagenesis and its Impact on Human Evolution

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DESCRIPTION

Spontaneous mutagenesis is a fundamental process in the evolution of species and the development of diseases, including cancer. In recent years, significant progress has been made in understanding the molecular mechanisms underlying spontaneous mutagenesis. DNA replication is a critical cellular process that ensures the constant transmission of genetic information from one generation of cells to the next. During replication, DNA polymerases synthesize a complementary strand of DNA based on the template provided by the original DNA molecule. These polymerases are remarkably accurate, with error rates estimated to be around one error per billion nucleotides incorporated. However, the absolute volume of DNA replication that occurs in a human cell presents a challenge. With over six billion base pairs in the human genome, each cell must accurately replicate its DNA thousands of times during its lifespan. Even with such low error rates per base pair, this still leads to a significant number of potential mutations due to the absolute magnitude of replication events.

DNA polymerases are the enzymes responsible for DNA replication. They catalyze the addition of nucleotides to the growing DNA strand and ensure the proper base pairing between the template strand and the incoming nucleotide. DNA polymerases have evolved advanced proofreading mechanisms to correct errors that occur during replication. However, these proofreading activities are not accurate and mutations can still arise. These polymerases are responsible for the bulk of DNA replication during cell division. DNA polymerase δ (Pol δ) and DNA polymerase ε (Pol ε) are the primary replicative polymerases in eukaryotic cells. They are known for their high accuracy but can occasionally make errors during replication. In addition to the replicative polymerases, cells also have specialized DNA polymerases that play key roles in various DNA repair processes. One such polymerase is *REV1* (also known as REV1-Polymerase ζ), which has unique properties related to Translesion Synthesis (TLS). *REV1* is a specialized DNA polymerase that is part of the *REV1*-Polymerase ζ complex. Unlike replicative polymerases, *REV1* is characterized by its ability to insert nucleotides opposite damaged DNA templates. This process, known as Translesion Synthesis (TLS), allows cells to bypass DNA lesions and continue replication. In TLS, when a replicative polymerase encounters a DNA lesion, it stalls. *REV1* is recruited to the site of the lesion, and it inserts nucleotides opposite the damaged site. This allows replication to continue past the lesion, even though the inserted nucleotide may not be a counterpart for the template.

REV1-Polymerase ζ is error-prone by design. It lacks the severe proofreading mechanisms of replicative polymerases, which makes it more likely to insert incorrect nucleotides during TLS. This inherent infidelity of *REV1* is essential for generating mutations, especially when DNA damage is encountered. While *REV1*-Polymerase ζ contributes to spontaneous mutagenesis, its activity must be tightly regulated. Too much mutagenesis can be detrimental, leading to genomic instability and diseases like cancer. Therefore, the cell tightly controls the advancing and activity of *REV1*-Polymerase ζ to strike a balance between error-prone TLS and constant DNA replication.

PRIMPOL (Primase-Polymerase) is another specialized DNA polymerase that plays a critical role in controlling spontaneous mutagenesis. Unlike REV1-Polymerase ζ, which primarily operates during TLS, *PRIMPOL* is involved in both replication and DNA repair processes. *PRIMPOL* is named for its primase activity, which allows it to synthesize short RNA primers needed to initiate DNA replication. This primase function is critical for the restart of stalled replication forks.

PRIMPOL also possesses polymerase activity, which enables it to extend the RNA primers it generates during replication restart. Importantly, *PRIMPOL* is capable of inserting nucleotides opposite damaged DNA templates, similar to *REV1*. *PRIMPOL*, like *REV1*, can introduce mutations during DNA replication and repair. However, *PRIMPOL* appears to be more accurate in nucleotide selection than *REV1*. This suggests that *PRIMPOL* may serve as a "guardian" against excessive mutagenesis by providing a less error-prone alternative to *REV1*-Polymerase ζ. The balance between mutagenesis and genomic stability is finely regulated in human cells. *REV1*-Polymerase ζ and *PRIMPOL*, along with other DNA polymerases, work in concert to maintain

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this balance. During TLS, *REV1*-Polymerase ζ is often the first responder to DNA lesions. It inserts nucleotides opposite the damage, but if the lesion is particularly challenging, other polymerases like *PRIMPOL* may be advanced to complete the synthesis. *PRIMPOL's* relatively higher accuracy may help correct errors introduced by *REV1*. Cells tightly regulate the recruitment and activity of both *REV1*-Polymerase ζ and *PRIMPOL*. This regulation ensures that these polymerases are only utilized when necessary, preventing excessive mutagenesis. Understanding the roles of *REV1*-Polymerase ζ and *PRIMPOL* in spontaneous mutagenesis has significant clinical implications, especially in the context of cancer.

Dysregulation of TLS and the excessive mutagenesis it can promote are associated with cancer development. Targeting the DNA repair pathways involving *REV1*-Polymerase ζ and *PRIMPOL* has emerged as a potential therapeutic strategy in cancer treatment. By selectively inhibiting these polymerases, it may be possible to sensitize cancer cells to chemotherapy or the radiation therapy. Understanding the genetic makeup of tumors, including mutations in DNA repair and replication genes like *REV1* and *PRIMPOL*, can guide precision medicine approaches. Modifying treatments based on a tumor's specific mutational profile may lead to more effective therapies.

CONCLUSION

Spontaneous mutagenesis is a complex and tightly regulated process in human cells. *REV1*-Polymerase ζ and *PRIMPOL* are key players in this process, contributing to both genomic stability and mutagenesis. The delicate balance between these two aspects is critical for maintaining the integrity of the genome while allowing for the evolution of species and adaptation to changing environments. Understanding the roles of these polymerases in spontaneous mutagenesis has far-reaching implications, from cancer development to potential therapeutic strategies and precision medicine approaches.