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Enduring Oncogene-induced Replication Stress: A Catalyst for Genomic Instability

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Introduction

Genomic instability, characterized by the accumulation of mutations, chromosomal rearrangements, and aneuploidy, is a hallmark of cancer. One of the key drivers of this instability is replication stress, a phenomenon that occurs when the replication machinery encounters obstacles that hinder the smooth progression of replication forks. Oncogene activation is a major source of replication stress, contributing to the acceleration of cell proliferation and the failure of DNA repair mechanisms. This article delves into the mechanisms of oncogene-induced replication stress, its role in promoting genomic instability, and the biological pathways that allow cells to tolerate and even exploit this stress to drive tumorigenesis. Oncogenes such as MYC, RAS, and CCNE1 are well-known inducers of replication stress. They cause cells to enter the cell cycle more frequently and replicate DNA at a faster rate than usual. This overdrive of the cell cycle machinery often leads to incomplete or stalled replication forks.

Replication stress arises when cells attempt to replicate DNA under conditions that limit the efficiency of this process, such as limited nucleotide availability, aberrant replication origin activation, or interference from transcription. Oncogenes such as MYC can cause the activation of additional replication origins to compensate for the high demand for DNA replication. However, this overloads the replication machinery, leading to collisions between replication forks or between replication and transcriptional machineries. These collisions can stall replication forks, leading to DNA strand breaks and incomplete replication, which are precursors to genomic instability. Oncogenes like RAS increase the speed of DNA replication by enhancing signaling pathways such as the RAS-RAF-MEK-ERK cascade, which promotes S-phase entry and accelerates cell cycle progression. The faster replication fork movement leaves less time for DNA repair mechanisms to correct errors, increasing the likelihood of mutations and structural DNA damage. The rapid replication also depletes nucleotide pools, further stressing the replication process [1].

Description

Oncogenes promote both excessive DNA replication and transcription, resulting in conflicts between these two processes. When replication and transcription collide on the same DNA template, replication forks can stall, leading to double-strand breaks. These unresolved DSBs contribute to chromosomal rearrangements, one of the most damaging forms of genomic instability. Oncogene activation often disrupts cell cycle checkpoints that would normally allow cells to repair replication-associated DNA damage before proceeding. For instance, overexpression of Cyclin E1 can drive cells through the G1/S checkpoint prematurely, leaving them vulnerable to replication stress and DNA damage during S-phase. Additionally, oncogene-driven inactivation of p53—a key tumor suppressor and guardian of the genome—compromises the cell's ability to respond to replication stress, further promoting genomic instability. The replication stress induced by oncogenes sets the stage for various forms of genomic instability, which serve as fuel for cancer evolution. Replication stress increases the rate of point mutations and indels (insertions/deletions), as errors introduced during DNA replication are not efficiently repaired [2].

If these mutations occur in proto-oncogenes, tumor suppressor genes, or genes involved in genome maintenance, they can drive cancer progression. Stalled replication forks and DNA strand breaks can lead to chromosomal translocations, inversions, and duplications. These rearrangements can result in the amplification of oncogenes, the deletion of tumor suppressor genes, or the creation of fusion proteins with oncogenic properties, all of which contribute to tumor development. Oncogene-induced replication stress can lead to improper segregation of chromosomes during mitosis, resulting in aneuploidy (an abnormal number of chromosomes). Aneuploidy is a common feature of cancer cells and can provide a growth advantage by increasing the dosage of oncogenes or decreasing the dosage of tumor suppressors. Genomic instability induced by replication stress often results in the missegregation of chromosomes during mitosis, leading to the formation of micronuclei—small, extranuclear bodies containing fragments of chromosomes. These micronuclei are prone to further DNA damage and contribute to ongoing genomic instability. Despite the detrimental consequences of replication stress, cancer cells are able to tolerate and survive it, primarily through the activation of stress response pathways. These pathways enable cancer cells to manage replication stress, repair DNA damage, and continue proliferating in the face of genomic instability [3].

The ATR kinase is a master regulator of the replication stress response. ATR is activated by single-stranded DNA at stalled replication forks, where it coordinates DNA repair and stabilizes the forks. ATR activates the downstream CHK1 kinase, which halts cell cycle progression and allows time for repair. Cancer cells frequently rely on the ATR-CHK1 pathway to manage replication stress, and inhibition of this pathway has been explored as a therapeutic strategy to selectively kill cancer cells while sparing normal cells. HR repair is a high-fidelity mechanism for repairing DSBs and resolving stalled replication forks. Key proteins in this pathway include BRCA1, BRCA2, and RAD51, which facilitate the repair of DNA breaks by using a sister chromatid as a template. Many cancers exhibit defects in HR repair, making them reliant on alternative, error-prone repair mechanisms such as non-homologous end joining [4].

Paradoxically, while HR deficiency promotes genomic instability, it also presents a therapeutic vulnerability. For example, PARP inhibitors target HR-deficient tumors by blocking the repair of single-strand breaks, leading to synthetic lethality. When replication forks encounter DNA lesions that cannot be immediately repaired, TLS allows replication to continue by using specialized polymerases that can bypass these lesions. Although TLS is an error-prone process that introduces mutations, it provides a short-term solution for cancer cells to avoid replication fork collapse. This mechanism helps cancer cells tolerate replication stress but also contributes to the accumulation of mutations and genomic instability. In addition to repairing damaged DNA, cells have evolved mechanisms to protect stalled replication forks from degradation. The proteins BRCA1, BRCA2, and FANCD2 stabilize stalled forks and prevent their collapse into DSBs. Cancer cells that retain fork protection capabilities are better able to survive replication stress, while those that lose these mechanisms experience heightened genomic instability. While genomic instability is a hallmark of cancer and drives tumor evolution,

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it can also be a source of vulnerability. Highly unstable genomes are often associated with poor prognosis, aggressive tumor behavior, and resistance to therapy.

However, cancer cells with extreme genomic instability may reach a tipping point where the accumulation of DNA damage becomes unsustainable, leading to cell death. This balance between the benefits and risks of genomic instability offers a unique opportunity for therapeutic intervention. Strategies that exacerbate replication stress or inhibit the DNA damage response pathways cancer cells rely on may push tumor cells beyond their tolerance threshold, inducing catastrophic levels of DNA damage. For example, inhibitors of the ATR, CHK1, and WEE1 kinases are being investigated as potential therapies that exploit replication stress in cancer. Given the central role of replication stress and genomic instability in cancer, targeting these processes has emerged as a promising therapeutic strategy. Inhibiting the ATR-CHK1 pathway sensitizes cancer cells to replication stress, leading to excessive DNA damage and cell death. ATR and CHK1 inhibitors are particularly effective in tumors with defects in other DNA repair pathways, such as HR-deficient cancers. PARP inhibitors are used to target cancers with HR deficiencies, such as BRCA1/2-mutant tumors. By blocking the repair of single-strand breaks, PARP inhibitors exacerbate replication stress and drive cancer cells to accumulate lethal levels of DNA damage. Combining replication stress-inducing agents (such as DNA-damaging chemotherapy or radiation) with DDR inhibitors may enhance the therapeutic efficacy. For instance, combining PARP inhibitors with ATR inhibitors or WEE1 inhibitors has shown promise in preclinical studies. Tumors with deficiencies in fork protection, such as those lacking BRCA1 or BRCA2, are particularly vulnerable to replication stress. Therapeutic strategies that target fork protection mechanisms or exacerbate fork degradation may selectively kill these tumors [5].

Conclusion

Oncogene-induced replication stress is a critical driver of genomic instability, fueling cancer progression by increasing mutation rates, promoting chromosomal rearrangements, and enabling tumor evolution. However, the ability of cancer cells to tolerate replication stress through various mechanisms presents both challenges and opportunities for therapy. By understanding the intricate relationship between replication stress, genomic instability, and tumor survival,

Acknowledgement

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Conflict of Interest

None.

References

1. Roos, Wynand P. and Bernd Kaina. "DNA damage-induced cell death: From specific DNA lesions to the DNA damage response and apoptosis." *Cancer Lett* 332 (2013): 237-248.
2. Jorgensen, Ine, Manira Rayamajhi and Edward A. Miao. "Programmed cell death as a defence against infection." *Nat Rev Immunol* 17 (2017): 151-164.
3. Hanahan, Douglas and Robert A. Weinberg. "Hallmarks of cancer: The next generation." *Cell* 144 (2011): 646-674.
4. Lee, June-Koo, Yoon-La Choi, Mijung Kwon and Peter J. Park. "Mechanisms and consequences of cancer genome instability: Lessons from genome sequencing studies." *Annu Rev Pathol* 11 (2016): 283-312.
5. Loeb, Lawrence A. "Mutator phenotype may be required for multistage carcinogenesis." *Cancer Res* 51 (1991): 3075-3079.

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