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Stalled Replication Forks under Replication Stress: Cellular Responses, Repair Mechanisms and Therapeutic Implications

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Abstract. DNA replication is essential for maintaining genome integrity during cell division. However, endogenous and exogenous factors frequently induce replication stress, leading to replication fork stalling and genome instability if unresolved. Recent studies have identified multiple mechanisms that coordinate replication fork stabilisation, protection and restart, although their regulation and roles in disease remain incompletely understood. This review summarises the current understanding of the mechanisms regulating stalled replication forks during replication stress. It first outlines the major endogenous and exogenous sources of replication stress before discussing the key cellular responses that maintain fork integrity, including Rad3-related (ATR)-checkpoint kinase 1 (CHK1) signalling, replication fork reversal and replication fork protection. Finally, it reviews the relationship between replication stress and cancer development, together with recent advances in therapeutic strategies targeting replication stress response pathways. Future studies should clarify the interactions among replication stress response pathways and develop more effective therapeutic approaches that selectively target replication stress in tumour cells.

Keywords: DNA replication, Replication Stress, Rad3-related (ATR)-checkpoint kinase 1 (CHK1) signalling

1. Introduction

DNA replication is a fundamental biological process that ensures the faithful transmission of genetic information during cell division. To maintain genome stability, the genome must be accurately duplicated once during each cell cycle. However, DNA replication is frequently challenged by endogenous and exogenous factors, collectively referred to as replication stress. Endogenous sources include DNA secondary structures, transcription–replication conflicts, reactive oxygen species (ROS), oncogene activation and depletion of deoxyribonucleotide triphosphate (dNTP) pools, whereas exogenous factors such as ultraviolet (UV) radiation, ionising radiation and chemotherapeutic drugs can also interfere with DNA synthesis. These obstacles can slow or stall replication fork progression, leading to genome instability if not properly resolved [1]. Since genome instability is a hallmark of cancer and many inherited disorders, understanding stalled replication forks has become an important topic in molecular biology and cancer research.

When replication forks encounter obstacles, cells activate a coordinated replication stress response. The ataxia telangiectasia and ATR-CHK1 signalling pathway is the central regulator of

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this response by sensing stretches of ssDNA coated with replication protein A (RPA), stabilising stalled replication forks, suppressing excessive origin firing and delaying cell-cycle progression to allow DNA repair [2]. Stalled replication forks can also undergo fork reversal, a protective remodelling process that converts the fork into a four-way junction-like structure, limiting replication-associated damage and facilitating repair or replication restart [3].

Recent studies have shown that multiple proteins cooperate to protect stalled replication forks from degradation. Breast Cancer Type 1 Susceptibility Protein (BRCA1) promotes homologous recombination (HR) repair and fork stabilisation, whereas RAD51 Recombinase (RAD51) protects reversed forks by preventing excessive nuclease-mediated degradation. Cells subsequently employ HR, translesion DNA synthesis and replication fork restart pathways to complete DNA replication [3]. In contrast, when fork protection fails, nucleases such as Meiotic Recombination 11 (MRE11) and DNA replication helicase/nuclease 2 (DNA2) excessively degrade newly synthesised DNA, resulting in replication fork collapse, chromosome breakage and genomic instability [4].

Replication stress is not only a major driver of tumour initiation and progression but also a therapeutic vulnerability in cancer. Cancer cells often experience elevated replication stress because of uncontrolled proliferation and oncogene activation, making them highly dependent on replication stress response pathways. Consequently, ATR inhibitors have attracted considerable attention because ATR coordinates the cellular response to replication stress, while Poly(ADP-ribose) Polymerase (PARP) inhibitors exploit defects in DNA repair to selectively eliminate cancer cells. Both approaches have demonstrated encouraging efficacy in preclinical studies and clinical trials [2]. Understanding the molecular mechanisms governing replication fork stalling, protection and repair may therefore facilitate the development of more effective targeted therapies and help overcome treatment resistance.

This review summarises the current understanding of replication stress-induced replication fork stalling, the molecular mechanisms underlying fork stabilisation, protection and repair, and recent advances in therapeutic strategies targeting replication stress in cancer..

2. Replication stress and replication fork stalling

2.1. DNA replication and replication fork structure

The carefully regulated process of DNA replication guarantees the accurate duplication of the genome before cell division. In eukaryotic cells, replication begins from multiple origins during the S phase of the cell cycle. Two replication forks that move bidirectionally along the DNA are established when the Cdc45-Mcm2-7-GINS (CMG) helicase complex unwinds the DNA double helix. RPA rapidly coats the exposed ssDNA to prevent secondary structure formation and protect it from degradation [1, 5].

At the dynamic replication fork, DNA synthesis and unwinding take place concurrently. After primer synthesis by DNA polymerase α/primase, DNA polymerase ε primarily synthesises the leading strand, while DNA polymerase δ discontinuously synthesises the lagging strand through Okazaki fragment formation [6]. Proliferating cell nuclear antigen (PCNA) and replication factor C (RFC) enhance polymerase processivity, while topoisomerases reduce torsional stress associated with replication. Together, these processes contribute to genomic stability and efficient replication fork progression.

Replication forks normally progress efficiently to duplicate the genome under typical circumstances. However, a number of obstacles can impede or stall fork progression, resulting in a condition known as replication stress. If appropriate protective mechanisms are not activated,

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persistent fork stalling may ultimately result in replication fork collapse and DNA double-strand breaks [1].

2.2. Sources of replication stress

Any situation that impedes the regular advancement of the replication fork is referred to as replication stress. It can result from extrinsic environmental influences as well as endogenous cellular processes [2].

One of the most frequent causes of replication stress is damage to DNA. DNA lesions that obstruct DNA polymerases and limit replication fork movement are produced by ROS produced during normal metabolism, UV radiation, ionising radiation, and some chemotherapy medications [7]. Replication stress can also result from DNA secondary structures such G-quadruplexes and hairpins, which offer physical barriers to replication and require specialised helicases to resolve [4].

Another important factor is the conflict between transcription and replication. Because DNA replication and RNA transcription can occur simultaneously on the same DNA template, collisions between the replication apparatus and RNA polymerase may halt replication forks. Moreover, persistent R-loops formed during transcription worsen replication stress by blocking fork advancement [7].

Replication can potentially be hampered by oncogene activation and inadequate dNTP availability. Oncogenes like MYC and RAS that are dysregulated lead to increased replication demand, excessive origin firing, and fork stalling. There are many different ways that replication stress can occur, but the outcome is usually the same: ssDNA buildup and slowed or stopped replication forks. Because unresolved halted forks can collapse into DNA DSBs, effective replication stress responses are essential for maintaining genome integrity [2].

3. Cellular responses to stalled replication forks

3.1. ATR-CHK1 signalling pathway

The principal cellular response to replication stress is the ATR-CHK1 signalling pathway, which is essential for preserving replication fork stability [8, 9]. Long segments of ssDNA may accumulate when replication forks stall because helicase activity may persist despite polymerase arrest [4]. RPA-coated ssDNA recruits the ATR–ATRIP complex, with ATRIP mediating the association between ATR and RPA-coated ssDNA.The replication stress response is coordinated by a signalling cascade that is started when activated ATR phosphorylates CHK1.

When the ATR-CHK1 pathway is activated, late origin firing is suppressed, cell cycle progression is slowed, and stalled replication forks are stabilised. This gives cells enough time to fix DNA damage before replication resumes. Replication fork collapse, an increase in DSBs, and extreme genomic instability are the outcomes of loss of ATR or CHK1 function. Inhibition of the ATR-CHK1 pathway has become a promising therapeutic approach in the treatment of cancer since many tumour cells undergo high levels of replication stress [8].

Other mechanisms are triggered to stabilise stalled replication forks and aid in their recovery if ATR-CHK1 signalling is insufficient to alleviate replication stress.

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3.2. Replication fork reversal

One crucial defence mechanism that enables cells to momentarily stabilise halted replication forks is replication fork reversal. Under adverse circumstances, the freshly synthesised leading and lagging strands anneal to one another instead of continuing DNA synthesis, and the parental DNA strands re-pair to create a four-way junction that resembles a "chicken foot" structure [3]. Replication fork reversal is facilitated by DNA translocases that remodel stalled replication forks, including ZRANB3, HLTF, SMARCAL1, and related DNA remodelling enzymes. These fork remodelling enzymes allow the processing and repair of replication-associated defects as well as the regression of halted replication forks by rearranging parental and nascent DNA strands. Fork reversal gives cells a chance to get around replication obstacles while also momentarily stopping DNA synthesis. Furthermore, before replication resumes, the reversed fork allows DNA repair pathways to address damage caused by replication [9].

Correctly regulated fork reversal also protects genome integrity, excessive or uncontrolled fork reversal could expose newly formed DNA to nuclease degradation. Replication fork protection systems are required because processing of reversed forks by nucleases like MRE11 and DNA2 without regulation causes nascent DNA damage [4]. Therefore, in order to achieve effective recovery and prevent unnecessary DNA damage, reversed forks need tight regulation.

3.3. Replication fork protection

For replication to successfully restart after fork reversal, newly synthesized DNA needs to be protected from deterioration. Some proteins work together to guard reversed replication forks from nucleases like MRE11 and DNA2. Replication fork protection is coordinated by a network of DNA repair proteins that stabilise stalled forks, inhibit nascent DNA degradation, and encourage replication restart. Main factors involve RAD51, BRCA1,as well as others HR proteins. The protective filament made up of nucleoproteins which RAD51 forms on freshly created DNA. BRCA1 and BRCA2 assist in recruiting and anchoring RAD51 at halted forks. FANCD2 provides additional fork protection through avoiding excessive breakdown of replication intermediates as well as coordinating repair processes tied to replication [3].

these proteins work together to prevent too much nuclease activity, protect growing DNA and allow replication restart to happen quickly. BRCA1 or BRCA2 loss causes reduced RAD51 mediated protection which results in increased nascent dna degradation creating replication fork instability resulting in genomic instability and cancer susceptibility [10].

When fork protection fails, replication fork collapse and genomic instability may result, possibly necessitating downstream DNA repair steps to re-establish replication. Thus, replication fork protection is considered a crucial mechanism that links replication stress responses to genome maintenance and cancer suppression.

4. Repair mechanisms of stalled replication forks

4.1. HR and replication fork restart

One-ended DSBs may eventually arise as a result of replication fork collapse brought on by prolonged replication stress that cannot be alleviated by fork stabilisation or protection. Non-homologous end joining is generally not the preferred pathway for these lesions because accurate

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replication restart requires homologous sequence information.Rather, HR is the main mechanism for re-establishing DNA replication and fixing collapsed replication forks [1].

The MRE11-RAD50-NBS1 (MRN) complex and CtIP mediate DNA end resection, which starts HR by producing 3' single-stranded DNA overhangs [3]. With the help of BRCA1, BRCA2, and other HR factors, RPA initially coats the exposed ssDNA before RAD51 replaces it. RAD51 nucleoprotein filaments subsequently promote strand invasion into the newly synthesised sister chromatid, which provides an undamaged homologous template for repair and DNA synthesis. HR minimises mutagenesis and chromosomal rearrangements while restoring DNA integrity with high fidelity by employing the sister chromatid as a template [3].

DNA helicases such as RECQ1 can restore DNA synthesis by remodelling reversed replication forks back into functional replication forks after replication-blocking lesions are removed [4]. Furthermore, when extended replication stress results in replication fork collapse, HR fixes the resulting DNA damage and reinstates functional replication forks. Replication restart is influenced by more than only HR, though [3]. If replication-blocking lesions cannot be removed immediately, cells may resort to repriming as a backup strategy. The primase-polymerase PRIMPOL allows replicative DNA polymerases to escape the damaged region and continue DNA synthesis by generating a fresh primer downstream of the lesion. Although this process creates single-stranded DNA gaps behind the replication fork, these gaps can subsequently be filled by post-replicative repair pathways, ensuring that genome duplication is completed on time [11].

In order to compensate for delayed or collapsed forks, cells can also activate latent inactive replication origins. Dormant origins frequently do not take part in DNA replication, despite being licensed during the G1 phase. By producing additional replication forks that rescue unreplicated genomic regions under replication stress, their activation reduces the risk of incomplete chromosomal duplication [12].

4.2. Nuclease-mediated processing

Stalled replication forks being processed under regulation by nucleases is a pivotal stage during replication fork recovery. A small amount of nucleolytic removal to remove the damaged DNA structures, thus allowing for HR repair But too many nuclease action can destroy brand new DNA and bring about replication fork breakage so regulation has to be accurate. MRE11 starts DNA end resection, dealing with reversed replication forks, so it's key nuclease in how replication forks get handled. Normally this results in efficient restarting and HR mediated repair of the replication fork. However if the protection of the replication fork is broken down like BRCA-deficient cells, then unchecked breakdown of babyDNA by MRE11 causes replication fork collapse which creates instability [13].

Additional nucleases can also help process replication forks in specific situations. DNA resection following MRE11 activity can be prolonged by the structure-specific endonuclease MUS81 cleaving persistent or unresolved replication intermediates and producing DNA ends that can be processed by repair pathways such HR, DNA2, and EXO1 [4, 13].

these nucleases are strictly controlled by replication fork protective agents like BRCA1 and HR etc. They prevent developing DNA from over damaged but also allow little processing so the fork can be quickly recovered. Thus balanced nuclease activity is essential to maintain genomic stability under replication stress [3].

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4.3. Translesion DNA synthesis

TLS provides an alternate strategy for overcoming replication-blocking DNA lesions when replicative DNA polymerases are unable to proceed with DNA synthesis. Instead of removing the DNA lesion before replication, TLS polymerases immediately synthesise DNA across damaged templates, allowing replication forks to avoid lesions and proceed with genome duplication [8].

By encouraging the recruitment and replacement of replicative polymerases with specialised TLS polymerases that can avoid replication-blocking DNA lesions, PCNA monoubiquitination initiates TLS. DNA synthesis can continue even in the presence of unrepaired lesions because the type of DNA damage dictates which polymerase is recruited. After bypass is finished, replicative polymerases restart regular DNA replication [14].

Although TLS reduces protracted fork stalling and replication fork collapse, the more error-prone nature of many TLS polymerases can add mutations, contributing to genomic instability and cancer evolution. Since many cancer cells depend on TLS pathways to withstand replication stress brought on by chemotherapy, TLS has become a viable target for combination therapies meant to overcome drug resistance [15].

5. Clinical significance and therapeutic implications

5.1. Replication stress in cancer

Replication stress is a feature of many cancers and has a dual role in tumour biology. On the one hand, persistent replication stress raises the burden of mutations, chromosome rearrangements, and DNA damage, all of which contribute to genomic instability and the development of tumours. However, a selective vulnerability that can be therapeutically exploited is created by cancer cells' increased reliance on replication stress response pathways [1]. Because tumour cells frequently function close to a threshold of tolerable replication stress, they are more susceptible to additional disruption of DNA damage response mechanisms than normal cells [2].

The therapeutic value of replication stress is particularly evident in cancers with abnormalities in DNA repair pathways. For instance, BRCA1/2-mutated breast and ovarian cancers depend more on alternative DNA repair mechanisms due to decreased HR and poor replication fork maintenance. Their synthetic lethality linked to HR failure causes their sensitivity to PARP inhibitors (PARPi), demonstrating how anomalies connected to replication stress may influence the choice of targeted therapy. In a similar vein, pancreatic ductal adenocarcinoma driven by KRAS shows elevated replication stress and may depend more on ATR-CHK1 checkpoint signalling to survive. Preclinical studies have shown that ATR inhibition can preferentially hinder the development of cancer cells with high replication stress, suggesting that targeting replication stress responses has therapeutic potential [16].

Therefore, in addition to being a product of oncogenic transformation, replication stress plays a significant role in defining tumour susceptibility. Finding cancers with high replication stress levels may enhance patient stratification and present chances to create more efficient, individualised treatments.

5.2. Targeted therapies

Replication stress has created new therapeutic opportunities by taking advantage of cancer cells' reliance on DNA damage response pathways. The ATR-CHK1-WEE1 signalling pathway and

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PARP-mediated DNA repair mechanisms are among the primary targets of current treatment approaches [1]. PARPi-based combinations have shown promising therapeutic potential among these strategies. In ovarian and triple-negative breast cancer models, preclinical research has demonstrated that combining PARPi with ATR, CHK1, or WEE1 inhibitors generates synergistic antitumour effects, particularly in PARPi-resistant tumour models. The EFFORT study reported a longer progression-free survival (6.8 vs. 5.5 months) for adavosertib plus olaparib compared with adavosertib alone, and the phase II CAPRI trial reported an objective response rate (ORR) of 46% (6/13) in platinum-sensitive ovarian cancer patients treated with ceralasertib plus olaparib after progression on prior PARPi therapy [2].

Single-agent checkpoint kinase inhibitors have also demonstrated activity in molecularly selected patients. The CHK1 inhibitor prexasertib achieved an ORR of 33% in BRCA-wild-type high-grade serous ovarian cancer, whereas the WEE1 inhibitor adavosertib produced an ORR of 29.4% with a median progression-free survival of 6.1 months. Responses were particularly favourable in tumours with CCNE1 amplification, ATM deficiency, or FBXW7 loss, highlighting the importance of genomic biomarkers for patient selection. However, dose-limiting haematological toxicities, including anaemia, neutropenia and thrombocytopenia, remain major challenges. Overall, current evidence suggests that biomarker-guided combination therapies are likely to provide greater clinical benefit than monotherapy while improving the management of replication stress-driven cancers [2].

5.3. Drug resistance and future perspectives

Even though PARPi have demonstrated significant clinical benefits, acquired resistance remains a major drawback, especially in tumours lacking BRCA1/2. Resistance mechanisms, such as secondary BRCA mutations restoring BRCA function, are linked to the restoration of HR repair [17].

Replication fork protection is one of the potential resistance mechanisms identified by current research. For instance, NSD3S was found to be a mediator of PARPi resistance in BRCA2-deficient prostate cancer cells. NSD3S was upregulated in PARPi-resistant cells and enhanced replication fork stability independently of HR restoration. Mechanistically, ATR-mediated phosphorylation recruited NSD3S to stalled replication forks, where it prevented PTIP-dependent recruitment of the nuclease MRE11 [18].

Crucially, PARPi sensitivity may be restored by targeting this resistance mechanism. Resistant BRCA2-deficient prostate cancer cells were rendered susceptible to olaparib by either pharmacological degradation using an NSD3-targeting PROTAC or depletion of NSD3S. In xenograft models, combination treatment with NSD3 PROTAC and olaparib dramatically decreased tumour growth when compared to PARPi monotherapy [18].

Therefore, in order to determine which patients are most likely to benefit from PARPi-based therapy, future research should go beyond single genetic indications and concentrate on thorough profiling of replication stress responses. Treatment durability may be increased and acquired resistance may be overcome with optimised medication combinations that target resistance-associated pathways, such as replication fork stabilisation mechanisms.

6. Conclusion

Cancer, as well as other human diseases, is affected by replication stress, which contributes to genomic instability. The article explained the mechanisms causing replication fork stalling and cellular responses that maintain fork integrity. Before examining replication stress responses like

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ATR–CHK1 checkpoint signaling, replication fork reversal, and fork protection, it first discussed the main endogenous and external sources of replication stress. These processes prevent replication fork collapse while preserving genome stability through DNA repair, restart, and fork stabilisation. Replication stress was also reviewed for its dual roles in tumour formation and cancer treatment and the potential of targeting replication stress response pathways.

The reaction to replication stress is not governed by one mechanism but by a coordinated network of cellular pathways. Understanding how these pathways interact can help develop targeted cancer treatments and improve knowledge of genome maintenance. Targeting replication stress response pathways could lead to better therapeutic outcomes with less toxicity to normal tissue.

Despite progress, barriers remain. Preclinical models have mainly elucidated regulatory systems, but their clinical significance has not been fully proven. In addition, interactions among replication stress response mechanisms remain unclear. Future research should define pathway interactions, identify reliable biomarkers for patient classification, and design treatment strategies that exploit replication stress in cancer cells. These efforts will enhance knowledge of genome maintenance and facilitate the use of replication stress research in treatment.

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