REVIEW

Rescue from replication stress during mitosis

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ABSTRACT

Genomic instability is a hallmark of cancer and a common feature of human disorders, characterized by growth defects, neurodegeneration, cancer predisposition, and aging. Recent evidence has shown that DNA replication stress is a major driver of genomic instability and tumorigenesis. Cells can undergo mitosis with under-replicated DNA or unresolved DNA structures, and specific pathways are dedicated to resolving these structures during mitosis, suggesting that mitotic rescue from replication stress (MRRS) is a key process influencing genome stability and cellular homeostasis. Deregulation of MRRS following oncogene activation or loss-of-function of caretaker genes may be the cause of chromosomal aberrations that promote cancer initiation and progression. In this review, we discuss the causes and consequences of replication stress, focusing on its persistence in mitosis as well as the mechanisms and factors involved in its resolution, and the potential impact of incomplete replication or aberrant MRRS on tumorigenesis, aging and disease.

Introduction

Genomic stability relies on accurate and complete genome duplication and faithful chromosome segregation during cell division. Cells are continuously exposed to exogenous or endogenous insults that may lead to DNA damage and challenge DNA replication. The eukaryotic cell has devised different mechanisms, known as DNA damage response (DDR), to detect, signal and repair DNA damage. The DDR involves a complex signaling cascade mediated by phosphatidylinositol 3kinase-related kinases (PIKKs), including DNA-dependent protein kinase (DNA-PK), ataxia telangiectasia-mutated (ATM), and ATM and Rad3-related (ATR) proteins. These sensor kinases phosphorylate a plethora of substrates, including DNA repair factors and checkpoint proteins, to coordinate DNA repair and chromatin modifications with cell cycle progression and cellular metabolic processes.¹ In addition to damaged templates, replication fork progression can be challenged by intrinsic obstacles such as difficult-to-replicate loci, highly transcribed genes, repeat sequences, non-canonical DNA structures or protein-DNA adducts.² All conditions that perturb DNA replication leading to replication fork stalling or slowing are collectively referred to as DNA replication stress. Replication stress induces a specialized branch of the DDR, the replication or S-phase checkpoint, triggered by the generation of stretches of single-stranded DNA at stalled or damaged forks, and depends on the activation of ATR and Chk1 checkpoint kinases.³⁻⁵ This pathway is fundamental to delaying cell cycle progression and allowing the cell to properly and timely repair damage, recover stalled replication forks, and complete replication before entry into mitosis. However, endogenous or low levels of replication stress or DNA damage, might not be sensed

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by the cell and escape checkpoint activation. Moreover, completion of DNA replication at certain genomic regions can be delayed up to G2 phase or even mitosis, leading to persistence of under-replicated DNA in mitosis, especially in replication stress conditions.⁶⁻⁸

Mitosis is the complex cellular process by which duplicated genetic material is equally distributed to 2 daughter cells.⁹ It begins with chromosome condensation (prophase), centrosome separation to form a bipolar spindle and attachment of the kinetochores to the spindle microtubules (prometaphase). By metaphase, all chromosomes become aligned on the metaphase plate and bioriented with respect to the spindle poles, which is essential for faithful segregation of the chromosomes into the daughter cells. Then, anaphase occurs, characterized by the separation and movement of sister chromatids toward the 2 opposite poles of the spindle. Mitosis ends with telophase, when the 2 sets of chromosomes reach the spindle poles and chromatin decondenses before cytokinesis physically separates the 2 daughter cells.

Mitotic defects leading to unequal chromosome segregation are a common cause of chromosomal instability (CIN) and cancer.¹⁰ Defective chromosome segregation and aneuploidy can be caused by dysfunction of the factors regulating proper assembly and dynamics of the mitotic apparatus, sister chromatid cohesion, bipolar attachment of kinetochores to the mitotic spindle and the spindle assembly checkpoint.¹¹ However, faithful chromosome segregation and maintenance of genome stability also depend on the coordination between genome duplication and cell cycle and mitotic progression. Recent studies have shown that under-replicated or unresolved DNA structures that form as

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a consequence of replication stress and persist into mitosis may hamper chromosome segregation leading to micronucleation and gain or loss of genetic material.¹²⁻¹⁴ They have highlighted the existence of pathways that operate not only during S-phase but also during mitosis to limit the deleterious consequences of replication stress and the transmission of DNA damage to daughter cells.¹⁵ Works from several groups have started to identify some of the factors and mechanisms involved.^{12, 13, 16-24} Collectively, they suggest that mitotic rescue from replication stress (MRRS) is a key process that must be tightly regulated to prevent structural and numerical chromosomal aberrations and avoid mitotic catastrophe and other deleterious outcomes of defective chromosome segregation. Therefore, we propose that exploring how cells respond to replication stress during mitosis may be crucial to understanding the mechanisms of replication stress-driven genomic instability. In this review, we discuss the causes of replication stress and the consequences of unresolved DNA damage or incomplete DNA replication, specifically in mitosis. We also present recent advances in the knowledge of the cellular response to under-replicated DNA in mitosis, with a specific focus on common fragile sites (CFSs). Finally, we discuss the different pathways involved in the rescue of DNA damage in mitosis and the consequences of their dysfunction on human health.

DNA replication program and the causes of replication stress

DNA replication is initiated at specific genomic loci called origins of replication.²⁵ It occurs bidirectionally and proceeds through the regulated and sequential firing of replication origins, leading to faithful and complete duplication of the chromosomes. Replication stress can be the outcome of a low density or inefficient activation of origins leading to long traveling and unstable replication forks, which makes origin-poor regions particularly sensitive to replication stress.²⁶⁻²⁹ Alternatively, replication stress can be the result of firing of an excessive number of origins, as a consequence of a defect in the developmental program of replication or the cellular replication timing program.³⁰ In such conditions, factors required for DNA replication, such as replication initiation factors, deoxyribonucleotides (dNTPs), the single-strand DNA binding protein RPA (replication protein A) and histones may become limiting, causing elongation problems and subsequent fork collapse.^{31, 32} The number of replication origins that are loaded (licensed) in G1 by the replicative MCM2-7 helicase is in excess with respect to the origins that are fired during a normal cell cycle.³³ A large fraction of them are passively replicated by forks coming from nearby origins and remain dormant in unperturbed conditions. However, they serve as back-up origins in case of replication fork stalling or slowing and become essential to ensure complete replication in replicative stress conditions.^{27, 34-36} If a replication fork stalls and DNA synthesis does not readily resume, stabilization of the arrested fork, which allows DNA to be replicated from an incoming adjacent fork, as well as firing of additional

origins locally to compensate for replication slowdown are both important mechanisms by which cells respond or adapt to replication stress.³⁷⁻³⁹ If stalling occurs at converging forks in a region lacking replication origins or at unidirectional forks, cells must rescue the fork. ATR, the central kinase involved in the replication stress response, not only delays cell cycle progression but also regulates origin firing and orchestrates many different pathways involved in fork stabilization, remodeling, and restart or repair of stalled or collapsed forks.^{4,40,41} The primary pathways that allow resumption of DNA synthesis in the event of replication obstacles include fork repriming, translesion synthesis or lesion bypass by template switching, fork remodeling/processing and fork restart by homologous recombination-mediated mechanisms.⁴² The choice of the pathway used to restart replication forks is a matter of intense investigation and likely depends on the type of the blocking lesion or DNA structure, the genomic or chromatin context, and the timing at which replication stalling occurs.

The different causes of replication stress have been recently reviewed.^{2, 32} Some examples of how replication fork progression and the replication program can be perturbed by exogenous or endogenous sources are described below.

Exogenous sources

Replication stress can be caused by agents that inhibit or block fork progression or cause DNA lesions. UV-light is an example of a physical agent that causes replication stalling by inducing pyrimidine dimers and blocking nucleotide incorporation by the replicative DNA polymerases.^{43, 44} Aphidicolin is a natural inhibitor of B-family DNA polymerases, and may slow-down or arrest DNA replication, leading to reversible replication stress.45-48 Chemicals used in anticancer chemotherapy and other genotoxic agents can cause DNA inter or intra-strand crosslinks, single-strand DNA breaks, base damage and DNAprotein crosslinks, that impede the elongation step of DNA replication.² Hydroxyurea (HU) is an anticancer agent that acts by inhibiting ribonucleotide reductase, the enzyme involved in nucleotide biosynthesis. HU is an example of how nucleotide depletion may lead to replication slow-down, change in origin usage, and progressive fork inactivation.^{49, 50} Origin overactivation may also be caused by histone deacetylase inhibitors that affect the 3-dimensional conformation of chromatin.^{51, 52} Other examples of chemicals causing replication stress are cisplatin and mitomycin C that induce DNA crosslinks, and camptothecin (or its derivatives topotecan and irinotecan) that inhibits Topoisomerase I activity.^{2, 53}

Endogenous sources

The cell is continuously facing a series of conditions that may limit its ability to replicate the entire DNA genome. Below is a list of several endogenous factors that may affect DNA replication and lead to genomic instability.

Difficult-to-replicate loci

These are genomic regions rich in di or tri-nucleotide repeats, palindromic sequences that tend to adopt cruciform

structures, and G-rich sequences that form structures called G-quadruplexes (G4).54-56 All these complex DNA structures constitute physical roadblocks to replication and can therefore act as replication fork barriers.54,56,57 A good example of difficult-to-replicate loci is the telomeres, the ends of linear chromosomes, composed of tandemly repeated sequences organized in a specialized nucleoprotein structure that protects them from degradation and from being recognized as DSBs by the DNA repair machinery, and ensures their maintenance in face of the "end replication problem," linked to the inability to fully replicate both strands of a linear DNA molecule.⁵⁸ Telomeric DNA may form G4 structures that are physiologically resolved by the DNA helicase RTEL1 and replicated with the help of Telomeric Repeat Binding Factor 1 (TRF1) and the homologous recombination proteins BRCA1 and 2.59-61 Moreover, telomeres are replicated unidirectionally and are therefore more prone to replication pausing. Similarly, the ribosomal DNA (rDNA) represents an example of a highly unstable locus, due to its complex genomic organization, high transcription density, and unidirectional replication.⁶²⁻⁶⁴ Studies on budding yeast rDNA have identified the existence of natural Replication Fork Barriers (RFBs), replication pause sites defined by specific DNA sequences that bind to non-nucleosomal proteins, blocking replication fork progression in the opposite direction to transcription and acting as recombinational hotspots.65-67 RFB-mediated mechanisms at rDNA loci to block replication in case of converging transcription, preventing head-on collisions between replication and transcription, have been identified in many organisms, including murine and human cells.^{64,68,69} Centromeres are also loci that are difficult to replicate due to their heterochromatic nature and richness in repetitive sequences.⁷⁰ Indeed, centromeric DNA forms looped structures and catenanes that are physiologically resolved by topoisomerase II α (TOP2A) in cooperation with the Bloom (BLM) protein complex.^{71, 72} Finally, replication can be blocked by DNA-bound proteins, such as pre-Replication Complexes (pre-RCs) bound on dormant origins, which under normal conditions are removed by specialized helicases, like Rmr3 in budding veast.54, 73

Activated oncogenes

Different studies based on precancerous lesions have shown that replication stress, fork collapse and consequent genomic instability can be induced by the activation of oncogenes.⁷⁴⁻⁷⁸ Replication stress and DNA damage following oncogene activation lead to a constitutive DNA damage response that induces cell senescence or apoptosis, thus protecting precancerous cells from becoming cancerous.^{74, 79-81} There are different ways by which oncogene activation can lead to replication stress.⁸² Activated oncogenes may alter the temporal program of replication and origin usage. For example, cyclin E activation leads to inhibition of pre-replication complex assembly and a decrease in origin firing, causing replication stalling and stress.⁸³ Contradictory with this finding, another study has shown that cyclin E overexpression impairs replication fork progression by inducing an excess of replication initiation and increasing conflicts between replication and transcription.⁸⁴ Deregulated origin

firing following overexpression of several oncogenes may also lead to exhaustion of replication factors. Consistently, it has been shown that oncogene activation results in nucleotide depletion that in turn causes replication stress.⁸⁵ Following this work, Xie et al. have shown that Bcl-2 activation leads to ribonucleotide reductase inhibition and consequent replication stress.⁸⁶ Collectively, these studies suggest that oncogeneinduced replication stress and DNA damage promote genomic instability and increase the selective pressure for mutations in p53 and DDR factors, which then allows cells to escape apoptosis and senescence, driving carcinogenesis.⁷⁵

Byproducts of cellular metabolism

Replication stress can also be caused as a result of DNA attack by byproducts of cellular metabolism.⁸⁷ The most important example of such products are free radicals including Reactive Oxygen Species (ROS) that may interfere with DNA replication. ROS can be the products of oncogene activation and can provide an alternative explanation for oncogene-induced replication stress.^{76, 88} Oxidative stress-induced DNA damage or alteration of the nucleotide pool can induce fork slowing and replication stress, leading to genomic instability.⁸⁹ Another source of endogenous replication stress are reactive aldehydes, which are the byproducts of alcohol metabolism and histone demethylation and may cause DNA inter-strand crosslinks or protein-DNA crosslinks, blocking DNA replication.^{90, 91} DNA lesions generated by reactive aldehydes have been shown to be critically dependent on a functional Fanconi anemia (FA) pathway for their repair, and deficiency in the enzymes that detoxify aldehydes act synergistically with FA pathway deficiency to induce genotoxic effects.92

DNA conformation and chromatin

Unwinding of DNA by topoisomerases is a pre-requisite for initiation of DNA replication. Problems in DNA unwinding may therefore block the DNA polymerase complex and cause replication stalling.⁹³ It has also been shown that the elongation step of DNA replication occurs in parallel with the redeposition of histones and the reestablishment of marks on the newly synthesized DNA.⁹⁴ Therefore, defects in the process of chromatin assembly may block completion of DNA replication, leading to fork collapse.⁹⁵ A recent study has shown that there is a tight regulation between histone synthesis and DNA replication, mediated by the elongation factor PCNA (Proliferating Cell Nuclear Antigen).⁹⁶ Finally, chromatin compaction and structural features of heterochromatin may also constitute an impediment to DNA replication.^{97, 98}

Transcription-replication conflicts

Another major source of replication stress and genomic instability are encounters between the replication and transcription machineries.⁶² The first method that eukaryotic cells adopt to avoid these collisions is spatial and temporal separation of the replication and transcription processes inside the nucleus.⁹⁹ If this separation does not occur, DNA polymerase progression can be blocked by the transcription machinery, leading to replication fork collapse and transcription-associated recombination.¹⁰⁰ A recent study has shown that the yeast ortholog of ATR, Mec1, together with the chromatin remodeler INO80 trigger the removal of RNA polymerase II from chromatin in HU-treated cells to avoid collisions between the transcription and replication machineries.¹⁰¹ An independent study has also highlighted the role of INO80 in RNA polymerase II release from chromatin under conditions of transcriptional stress.¹⁰² Interference between transcription and replication may also result in complementary binding between the newly synthesized RNA and one of the 2 replicating DNA strands.^{103, 104} These RNA-DNA hybrids, called R-loops, are favored at CG-rich loci and are resolved by endogenous RNase H or specialized helicases, such as Senataxin and Aquarius^{105, 106}. If not resolved, R-loops may lead to fork collapse and replication stress. RNA-DNA hybrids can form cotranscriptionally and are increased when transcription elongation or mRNA processing is impaired.¹⁰⁷⁻¹⁰⁹ R-loops can also result from hybridization in trans of RNA molecules with complementary DNA, which in yeast is promoted by homologous recombination proteins.¹¹⁰ R-loops have important functions in epigenetic regulation and gene expression¹¹¹ but can induce genomic instability when they are deregulated or in excess.¹¹² Moreover, transcription may impede replication by inducing topological stress, which requires topoisomerase activity to prevent R-loop accumulation and genomic instability.^{113, 114} Topological constraints can also be promoted by nuclear organization and higher order chromatin organization. For example, increased torsional stress accumulates at regions localized at the nuclear pores, where mRNA processing occurs.¹¹⁵

Fragile sites

Chromosome fragile sites (FSs) are genomic regions that recurrently appear as gaps, breaks or constrictions on metaphase chromosomes.¹¹⁶ The cytogenetic manifestation (or "expression") of FSs was found to be induced in particular culture conditions, such as in folate- or thymidine-poor media.¹¹⁷ FSs are classified as common or rare based on their frequency in the population.¹¹⁶ Rare fragile sites are expressed in a small percentage of individuals (less than 5%), are inherited in a Mendelian manner, and their instability is associated with the expansion of trinucleotide repeats or AT-rich minisatellites; conversely, common fragile sites (CFSs) are present in all individuals, and thus, represent normal components of the chromosome structure that become unstable in replicative stress conditions. CFSs can be induced in vitro by exposing cells to low doses of aphidicolin or by altering the pool of nucleotides.^{45, 118} They are located at late-replicating histone-hypoacetylated regions of the genome, and most of them are found within long genes, spanning from several hundred Kb up to 4 Mb in length.^{116, 119-121} The sensitivity of these sites to breakage following replication stress is strongly dependent on cell type, suggesting that the DNA sequence is not sufficient to elicit their fragility, but the replication timing, the origin density, the transcription program and epigenetic factors may also define the characteristics of CFSs.¹²²⁻¹²⁵

Several non-mutually exclusive mechanisms can explain the basis of CFS fragility at the molecular level. The first is based on the fact that these regions are located at late replicating domains comprising AT-rich sequences that can form secondary structures and may block or delay DNA replication.¹¹⁶ Moreover, CFSs are characterized by a paucity of active

replication origins so that, in conditions of replication slowdown, the neighboring forks have to travel long distances and may not be able to complete replication before mitosis.^{28, 29, 122,} ¹²⁶ In addition, CFSs are often located within long genes that are transcribed over more than one cell cycle and their breakage is correlated with their transcription, indicating that CFS fragility can be induced by collisions between replication and transcription machineries and R-loop accumulation.¹²⁷ Indeed, Copy Number Variants (CNVs) that are often the outcome of chromosomal instability have been shown to overlap with CFSs and, in particular, with those localized at long, actively transcribed genes.¹²⁸ This would suggest that CNVs and CFSs are actually different manifestations of transcription-replication conflicts. Interestingly, it has been shown that transcription may displace MCMs bound to origins, causing a reduced number of licensed origins or inactivation of dormant origins, thus leading to origin paucity or to inefficient back-up of CFS replication in conditions of replication stress.¹²⁹⁻¹³¹ CFS instability is also induced by aberrant oncogene expression.77, 132 The Kerem group has shown that different oncogenes elicit different fragility landscapes in the same cells, revealing the complexity of the mechanism that regulates the stability of CFSs.^{125, 133} Interestingly, a recent study has identified a new class of fragile sites, called early-replicating fragile sites (ERFS), located in highly transcribed GC-rich repeat-containing genomic regions, causing many recurrent genome amplifications and deletions in B-lymphocytes,¹³⁴ further supporting a role for the interplay between replication and transcription in generation of fragility. Therefore, it would be of interest to understand whether breakage could be the result of persistence and/or mitotic processing of stalled forks or other types of intermediates formed as a consequence of replication-transcription conflicts.

Consequences of replication stress in mitosis

Despite the fact that replication fork impediments are normally sensed and managed by cells, endogenous or low levels of replication stress, induced, for example, by low doses of aphidicolin, may not be detected by the cell or may be tolerated, preventing the full activation of a checkpoint response.3,135,136 In such cases, cells do not arrest in S-phase to complete replication but proceed into mitosis with under-replicated DNA or unresolved DNA structures.^{12,13,15} Inactivation or dysfunction of dormant origins of replication induces a certain level of replication stress that may also lead to progression through mitosis with incomplete DNA replication.²⁷ These conditions result in persistence in mitosis of joint molecules (JMs) comprising under-replicated DNA, catenated DNA duplexes or unresolved DNA replication/repair intermediates that impede sister-chromatid disjunction.^{24, 137} If not timely and safely processed, these latent JMs generate chromosome entanglements and segregation defects, leading to genomic instability. The most common consequences of replication stress that persist in mitosis are described below.

Multipolar mitoses

In addition to challenging genome duplication and chromosome disentanglement, endogenous or low levels of replication stress may also globally affect mitosis and chromosome segregation by inducing over-duplication of the centrosomes, leading to the assembly of mitotic spindles with multiple poles.¹³⁸⁻¹⁴¹ Interestingly, it was shown that supernumerary centrosomes arise spontaneously in homologous-recombination (HR)-deficient cells as a result of decreased fork speed and can be rescued by nucleoside supplementation.¹⁴⁰ Although the molecular link between replication stress and centrosome duplication remains unknown, an interesting study showed that Chk1 is localized at the centrosomes of interphase cells to prevent centrosome separation, activation of Cdk1 and entry into mitosis.¹⁴² A prolonged S-phase that does not activate a full Chk1-dependent cell cycle arrest may, therefore, lead to centrosome over-duplication, with detrimental consequences in the following mitotic phase.

Anaphase bridges

Anaphase bridges are defined as DNA connections linking the segregating chromosomes during anaphase. Chromatin bridges or bulky anaphase bridges can be detected with classical DNA ligands, are histone-bound and represent the physical link between 2 incompletely separated sister chromatids or joined chromatids/chromosomes. Recently, a new class of anaphase bridges has been discovered, called Ultra Fine Bridges (UFBs).¹⁴³ UFBs are thin DNA bridges that, in contrast to the bulky bridges, cannot be stained with conventional DNA dyes (such as Hoechst or DAPI) and are devoid of histones. This might indicate that they contain a partially denatured, single-stranded, or stretched DNA conformation that is either not detectable or not permissive to intercalating agents.¹⁴⁴ UFBs were first observed by immunofluorescence staining of proteins coating these DNA threads in anaphase, specifically, the Bloom syndrome helicase (BLM) and the Plk1-interacting checkpoint helicase (PICH), which were shown to colocalize on those structures.^{16, 19} A portion of these bridges is also bound by the ssDNA binding protein RPA.^{13,145}

There are at least 3 major classes of UFBs.¹⁴⁶ First, the centromeric UFBs (c-UFBs) that are usually formed after incomplete chromatid disjunction at centromeric regions and are marked by kinetochore proteins, such as Hec1.^{12,16,19} The existence of these UFBs can be attributed to the complexity of the DNA sequences at these regions (see the section above) or to the increased centromeric chromatid cohesion, creating DNA catenanes that are difficult to resolve.¹⁴⁷ The c-UFBs are the most prevalent class of UFBs and are commonly observed in anaphase cells even in unperturbed conditions. They are induced by treatment with Topoisomerase II inhibitors, indicating that they most likely arise from incomplete decatenation of duplex DNA molecules.^{19,148,149} Another class includes UFBs that do not have centromeric origin, but instead, they represent areas of DNA that have not been completely replicated or late replication/recombination intermediates that have not been resolved and preferentially arise at fragile site loci (fs-UFBs).^{12,13} These UFBs are rarely observed in unperturbed conditions but are induced after treatment with agents that inhibit replication, such as aphidicolin or mitomycin C, and are characterized by the binding of the Fanconi anemia (FA) proteins FANCD2 and FANCI, not across the bridge but at their termini.^{12, 13} Consistent with the role of replication stress and DNA damage in inducing this type of bridges, the tips of the fs-UFBs and their precursors are often positively stained for gammaH2AX.^{12, 13} The third class of UFBs comprises the t-UFBs that derive from chromosome entanglements at telomeric loci. t-UFBs are rarely observed in normal conditions, but they are induced when proteins involved in telomere replication and maintenance are dysfunctional, such as the Werner syndrome helicase (WRN), the telomeric proteins TRF1 and TRF2, or the Taz1 fission yeast ortholog of human TRF1/TRF2.150-153 Although the exact nature of the structures underlying UFBs is still unclear, it is thought that c-UFBs represent the physiologic manifestation of late decatenation of centromeric DNA and may contribute to generation of the proper tension between sister chromatids to promote correct segregation of chromosomes during anaphase,¹⁴⁹ while the other UFB forms are likely the result of under-replicated DNA that persists at difficult to replicate loci as a consequence of delayed replication or fork stalling in the presence of repetitive DNA, G-quadruplexes, R-loops, or tightly bound protein-DNA complexes, similar to what is reported for replication fork barriers in yeast.^{145,154} Indeed. telomeres behave as fragile sites in the absence of TRF1, and telomere fragility can be induced by aphidicolin.^{60, 155}

UFBs may, therefore, derive from catenanes, hemicatenanes or other types of replication/recombination intermediates resembling Holliday junctions, which form independently from and are mostly prevented by RAD51.^{13,} ¹⁴⁵ UFBs are bound at the transition between metaphase and anaphase by the BTRR complex, formed by the BLM helicase, Topoisomerase IIIa, RMI1 and RMI2, which likely act to resolve UFBs through unwinding of late replication intermediates, decatenation of hemicatenanes, or dissolution of recombination intermediates.¹³⁷

PICH is a DNA translocase with ATPase activity that is recruited to DNA after nuclear envelope breakdown in prometaphase.^{19,144} PICH is needed during prometaphase and metaphase for proper chromosome condensation and architecture, and this function is distinct from its function during anaphase.^{156,157} Interestingly, it has been shown that PICH binding to DNA is enhanced by tension-induced DNA stretching, which may explain the ability of PICH to bind to UFBs.¹⁴⁴ In addition, it has been shown that the ATPase activity of PICH is specifically required to prevent chromatin bridges but is dispensable for UFB resolution, suggesting that these 2 types of bridges may have different origins.¹⁵⁷ PICH has been proposed to function by preventing histone binding to areas that need to be repaired during mitosis, leading to the formation of UFBs.¹⁵⁶ A recent study has revealed that PICH has a role in attracting and activating the decatenase activity of TOP2A at highly repetitive loci, such as at rDNA and centromeric regions.¹⁵⁸ Following this work, it has been shown that, similar to centromeric DNA, rDNA may also undergo delayed decatenation and form PICH-stained anaphase bridges, which are induced by Topoisomerase II inhibition, thus identifying another class of UFBs.¹⁵⁹ Other clues regarding the nature and origin of UFBs have come from the identification of additional

proteins that bind to these structures and are important for their resolution, including TOP2A, Topoisomerase II β -binding protein 1 (TopBP1), FANCM and Rif1. TopBP1, a protein involved in replication initiation, checkpoint activation and DNA repair, has been shown to bind and resolve anaphase bridges through an interaction with TOP2A.^{145,160} The Fanconi anemia protein FANCM, a DNA translocase with branch migration activity, has also been shown to bind to UFBs, but only in late anaphase and telophase cells, where it replaces BLM, suggesting that it might have a role in resolution of persistent UFBs.¹⁶¹ Interestingly, a recent study has shown that Rif1, a protein with multiple roles in replication timing, telomere replication and DSB repair,¹⁶² colocalizes with PICH and BLM primarily on c-UFBs, but it has also been found to be recruited to APH-induced FANCD2-positive UFBs, suggesting that it localizes to UFBs independently from their origin.¹⁶³ In yeast, however, Rif1 has been shown to have a double-edged role in UFB processing because it prevents the resolution of t-UFBs while promoting the resolution of other non-telomeric UFBs, suggesting that UFBs of different origins may be channeled into different pathways or require different mechanisms for their resolution.¹⁵³

Under normal conditions, the majority of UFBs are resolved by late anaphase and telophase. Persistent UFBs may carry out some form of unresolved DNA damage or undergo breakage (either by mechanical stress at the cleavage furrow or by controlled endonuclease activity)¹⁶⁴ and transition into 53BP1 (p53 binding protein 1)-positive nuclear structures, called 53BP1 bodies, that are thought to shield DNA lesions in G1.^{17,18,23} However, when not resolved in a timely manner or when they are in excess, persistent chromosome entanglements, chromatin bridges and UFBs can have detrimental consequences in terms of cell homeostasis and genome stability.

Rescue of under-replicated/unresolved DNA during mitosis

It is intriguing that, under endogenous or mild replication stress conditions, cells escape from checkpoint activation and proceed to G2, or even mitosis, with areas of incomplete replication.

It would be meaningful to determine why low levels of DNA damage or under-replicated DNA do not elicit cell cycle arrest,³ whether threshold levels are tolerated, or whether a mechanism of adaptation is at work to allow cells to progress into mitosis, as initially proposed in yeast.¹⁶⁵⁻¹⁶⁷ Interestingly, a recent work has shown that one essential function of ATR in unperturbed growth conditions is controlling the timing of cell cycle progression and preventing premature entry into mitosis, thereby keeping low threshold levels of under-replicated DNA at the onset of mitosis.¹⁶⁸ Indeed, it has been shown that yeast cells can proceed to anaphase with incomplete DNA replication, even in the presence of an active checkpoint.¹⁶⁹ Likewise, a series of recent studies in metazoans have shown that some underreplicated chromosomal regions remain, even after entering into mitosis. The cells have developed different mechanisms to resolve these structures during mitosis to prevent chromosome mis-segregation.¹⁵ Below, we describe the

mechanisms and pathways that have recently been determined to play a role in the resolution of under-replicated DNA during mitosis.

FA pathway and its roles in the replication stress response

FA is a rare genetic disease characterized by developmental abnormalities, bone marrow failure and cancer predisposition, caused by mutations in at least 20 *FANC* genes.¹⁷⁰⁻¹⁷² The FA proteins constitute a pathway involved in the replication stress response and repair of interstrand crosslinks (ICL). Most FANC proteins form the FA core complex that primarily acts as a ubiquitin ligase to mono-ubiquitinate FANCI and FANCD2, which form a heterodimer called the ID complex and promote ICL repair by the coordinated action of endonucleases, TLS polymerases and homologous recombination proteins. The cells of FA patients display hypersensitivity to ICL and an increased frequency of spontaneous and ICL-induced chromosomal aberrations and radial chromosomes.

Recent works have shown that FA proteins, apart from their role in ICL repair, have an important role in maintaining genomic stability after replication stress, or even during normal replication, by regulating origin firing, replication fork stability and restart. FANCD2 and HR proteins have been shown to stabilize replication forks after HU treatment and protect nascent DNA from nucleolytic degradation.¹⁷³ In addition, FANCD2 and FANCI have been isolated on nascent DNA at stalled replication forks,^{174,175} and FANCI also binds to unperturbed, active forks.¹⁷⁵ FANCD2 interacts with MCM proteins, independently from its monoubiquitination by the FA core, and restrains DNA synthesis in conditions of nucleotide deprivation, thus preventing ssDNA accumulation and promoting recovery from replication stress.¹⁷⁴ Moreover, it has been shown that FANCI and FANCD2 have independent opposing roles in conditions of low replication stress: FANCI is required for activation of dormant origins to enable the timely completion of DNA replication before mitosis, whereas FANCD2 inhibits origin firing and restrains DNA synthesis.¹⁷⁶ The functions of these proteins are ATR-dependent because, in conditions of high replication stress, ATR phosphorylates FANCI to allow binding to FANCD2 and suppression of origin firing. The FANCD2-FANCI heterodimer then binds to chromatin and is monoubiquitinated to promote fork repair and restart.¹⁷⁶⁻ ¹⁷⁸ In addition, recent studies have highlighted the role of HR and FA proteins in regulating the conflicts between replication and transcription.¹⁷⁹⁻¹⁸³ FA-deficient cells were shown to accumulate R-loops and DNA breaks, which could be prevented by RNase H or transcription inhibitors.^{182,183} Garcia Rubio et al. also showed that FANCM translocase activity was required for R-loop suppression.

Consistent with its role in preventing or resolving replication problems, the FA pathway regulates CFS replication and stability.^{184,185} The function of FA proteins extends beyond S-phase.¹⁵ If recovery from replication stress in S-phase is not successful or incomplete, FANCD2 and FANCI persist at CFSs on mitotic chromosomes even up to telophase.^{12,13} Although the function of FA proteins in mitosis remains unknown, they have been shown to promote BLM-mediated resolution of aphidicolininduced, non-centromeric (Hec1-negative) anaphase bridges, limiting chromosome mis-segregation and aneuploidy.¹² In addition, FANCM is recruited to UFBs in late telophase and likely contributes to bridge resolution.¹⁶¹ Although it is not clear how FA proteins fulfill their role, the functional crosstalk between the FA pathway and BLM in response to replication stress may be important in both S-phase and mitosis.^{12,186-188} During mitosis, BLM exerts its function in concert with Topoisomerase III α to promote complete sister chromatid disjunction and UFB resolution.¹⁶ Because FANCD2 and FANCI do not bind across bridges but to their extremities, they might have a role in stabilizing the DNA structure or regulating the chromatin environment in a way that promotes UFB resolution. Further work will be required to solve this issue.

Structure-selective endonucleases and their role at fragile sites

The XPF/MUS81 family of structure-selective endonucleases are nucleolytic enzymes that recognize and cleave specific DNA structures instead of DNA sequence elements.¹⁸⁹ MUS81 is the catalytic subunit of a cell cycle-regulated structure-selective endonuclease involved in interstrand crosslink repair, homologous recombination and replication fork restart. It forms a complex with EME1, its regulatory subunit, and the MUS81-EME1 complex acts by cutting 3' flaps, D-loops, branched DNA structures and Holliday junctions. ERCC1, which forms a complex with XPF, is another structure-selective endonuclease that is involved in nucleotide excision repair and interstrand crosslink repair, cleaving bubble-like structures, stem-loops and 3' flaps. In mouse embryonic stem (ES) cells, Mus81-Eme1 has been shown to bind to stalled replication forks and induce DNA breaks that are essential for the recovery of the forks.¹⁹⁰

Recently, 2 studies have revealed an interesting role for MUS81-EME1,^{20 21} and ERCC1²⁰ in processing under-replicated or unresolved DNA structures at CFSs in mitosis. Specifically, these studies have shown that, following mild replication stress, these endonucleases are recruited and cut DNA at CFSs to resolve replication intermediates and prevent the formation of anaphase bridges. They are recruited to CFSs and colocalize with FANCD2 foci from late G2 or early prophase, when the chromosomes start to condense, until the metaphase to anaphase transition,^{20,21} suggesting that their action is required to release chromosome interlinkage before anaphase. Intriguingly, depletion of MUS81 and ERCC1 was associated with a decreased frequency of CFS gaps and breaks in metaphase but a concurrent increase in chromatin bridges and UFBs, as well as mitotic catastrophes and accumulation of DNA breaks and 53BP1 bodies in G1, indicating that, even if breakage at CFSs in mitosis can potentially lead to genetic instability, tightly controlled endonuclease activity of MUS81 and ERCC1 prevents chromosome mis-segregation and transmission of DNA damage to daughter cells.^{20, 21}

In addition to the endonucleases described above, subsequent works have revealed a role for the scaffold protein SLX4 during mitosis in regulation of CFS stability and prevention of anaphase bridges, via its newly reported SUMO-binding,^{191, 192} and SUMO ligase activity.¹⁹¹ SLX4 is an FA protein that serves as a binding platform for MUS81-EME1 and XPF-ERCC1 and has an essential role in ICL repair.¹⁹³ Guervilly et al. showed that SLX4 colocalizes with MUS81 and ERCC1 in mitotic cells and is required for their recruitment, which suggests that SLX4 acts in the same pathway as the MUS81-EME1 and XPF-ERCC1 endonucleases and promotes controlled DNA processing at CFSs before anaphase, to prevent chromosome mis-segregation and mitotic catastrophe.¹⁹¹

Unscheduled DNA synthesis in late G2 to early mitosis

Several studies have demonstrated that the cell is able to resolve incompletely replicated DNA structures that persist in mitosis and that this can occur even at the last-minute, just before entry into anaphase, to prevent chromosome mis-segregation and its detrimental consequences. By pulse-labeling cells with the thymidine analog ethynyldeoxyuridine (EdU), the Hoffmann and Rosselli groups have shown that active DNA synthesis can occur in late G2 or early mitosis.^{6, 20} The EdU incorporation was observed, though very rarely, even in unperturbed mitotic cells but was significantly induced after treatment of cells with low-doses of aphidicolin.⁶ Moreover, this type of unscheduled DNA synthesis was increased in cells deficient for the TLS polymerase $Pol\eta$, which was shown to contribute to CFS replication in S-phase, preventing CFS instability.⁶ The majority of sites showing EdU incorporation in mitotic cells corresponded to the chromosome loci targeted by FANCD2 and endonucleases, indicating that completion of DNA replication at CFSs and possibly other genomic regions can be delayed until mitosis.⁶ ²⁰ In line with these findings, several independent studies have shown that replicative or repair DNA synthesis at late replicating or challenging loci in early mitosis represents a last attempt to complete genome duplication and limit under-replicated DNA and mitotic defects.^{22, 23, 168, 194-196}

TopBP1-dependent mitotic DNA synthesis

The Lisby laboratory has demonstrated the existence of active unscheduled DNA synthesis in mitosis, by showing Topoisomerase II β -binding protein 1 (TopBP1)-dependent incorporation of nucleotides in mitotic cells.²³ The authors showed that TopBP1 colocalizes with FANCD2 foci in early mitosis after mild replication stress and is required for SLX4 binding to chromatin. TopBP1-dependent DNA synthesis is known to occur after mitotic onset because a mutant TopBP1 protein lacking the nuclear localization signal, therefore only capable of accessing chromatin after breakdown of the nuclear envelope, rescued the reduced EdU incorporation observed in TopBP1deficient cells.²³ Taken together, these data suggest that the cell is able to complete DNA synthesis in mitosis, in the presence of condensed chromatin, at regions of delayed replication forks. Interestingly, TopBP1 not only localizes with the APH-induced FANCD2-targeted sites but also forms spontaneous foci at other chromatin loci in mitotic cells independently from replicative stress; even if these structures do not seem to be linked to replication stress, TopBP1-mediated resolution is necessary

to prevent 53BP1 nuclear body formation and transmission of DNA damage to daughter cells.²³

Break-induced replication (BIR)

Recently, the Hickson group has shown that replication stress induces POLD3-dependent DNA synthesis in mitosis, which is promoted upon cleavage of replication forks at CFSs by the MUS81-EME1 in complex with SLX4.²² Specifically, by showing EdU incorporation at CFSs in mitotic cells after a G2-block, they demonstrated a chromatin condensation-dependent mechanism of DNA synthesis that occurs during the transition of cells from G2 to prophase and early prometaphase. POLD3 (pol32 in yeast) is a regulatory subunit of DNA polymerase δ required for break-induced replication (BIR), a well conserved HR-mediated mechanism that utilizes a single-ended DSB to restart replication at broken or collapsed forks and to maintain eroded telomeres.¹⁹⁷⁻¹⁹⁹ BIR has been most well characterized in yeast, where it has been shown to comprise different sub-pathways that can be Rad51-dependent or independent.^{197,198} In contrast to the canonical HR pathway, BIR is an errorprone type of HR, often based on very short sequences of homology and prone to fork stalling and template switching events (called micro-homology mediated BIR or MMBIR or FoSTeS), leading to chromosome duplications, copy number variations (CNVs) and gross chromosomal rearrangements (GCRs).^{197,200} How this pathway is regulated during mitosis is not known. It has been shown that CFS-associated intermediates form independently of RAD51,13,139,201 and that HR proteins, such as BRCA1, RAD51 and BLM, are inactivated by CDK1-mediated phosphorylation and dissociate from the chromatin by late G2.^{12,13,202} In addition, DSB repair in mitosis has been shown to be inhibited to avoid aberrant joining of chromosome ends.^{203,204} This suggests that BIR-mediated rescue of stalled forks at CFSs in mitosis would rely on a RAD51-independent pathway, likely as a backup mechanism.²⁰⁵

The activity of MUS81 is increased through phosphorylation of its binding partner EME1 by CDK1 in G2-M, providing a way to fine tune regulation of its enzymatic activity.²⁰⁶ Indeed, it has been shown that oncogenic stress induces premature MUS81 activation, leading to aberrant processing of reversed replication forks and generation of toxic replication intermediates.²⁰⁷ Endonucleases may participate in multiple steps during BIR to generate or displace the strand invasion intermediate, cleave flap structures, restore an active fork and resolve recombination intermediates.²⁰⁸ Work in yeast has shown that the BIR pathway can be promoted in the absence of Mus81 and Yen1 endonucleases²⁰⁹ and that Mus81 may restrain BIR and suppress template switching.²¹⁰ Therefore, it would be interesting to determine how the endonuclease complexes are recruited and regulated and whether other pathways participate in rescue from replication stress at CFSs and possibly other loci during mitosis. In this context, SLX4 and its SUMO-related functions may be a central regulator of MRRS.²¹¹ During ICL repair, the FA pathway has been shown to promote endonuclease recruitment to damaged DNA and ICL unhooking.²¹² However, MUS81 and ERCC1 recruitment to mitotic chromosomes has

been shown to occur independently of FA pathway activation.²⁰ Using chicken DT40 cells deficient for FANCD2, Pedersen et al. also showed that SLX4 foci assembly in mitosis is independent from FANCD2.²³ Interestingly, TopBP1 was shown to be required for SLX4 recruitment and mitotic DNA synthesis.²³ However, it is still unclear whether DNA synthesis at these sites occurs by a homologous recombination (HR)-mediated mechanism or by simple loading of DNA polymerases. Since chicken cells lack a MUS81 ortholog,¹⁸⁹ another endonuclease or another mechanism must be responsible for mitotic synthesis in these cells.

Translesion synthesis (TLS)

TLS is a damage tolerance mechanism alternative to HR that addresses replication stress induced by stalling of the replicative DNA polymerases at various lesions on template DNA.²¹³⁻²¹⁵ It is an error-prone process that allows DNA replication by directly bypassing the DNA lesions. It is mediated by specialized low-fidelity DNA polymerases, such as Pol η and Pol ζ , that are recruited to chromatin by monoubiquitinated Proliferating Cell Nuclear Antigen (PCNA) and the polymerase scaffold protein Rev1.^{216,217} A study by the Hoffmann laboratory showed that $Pol\eta$ is required for DNA synthesis at CFSs during S-phase, to allow timely completion of DNA replication before entry into mitosis.⁶ In line with this work, a study by the Kupfer group showed that a non-ubiquitinated form of FANCD2, in a complex with RAD51 and the E3 ubiquitin ligase Rad18, is required for PCNA monoubiquitination and $Pol\eta$ assembly onto chromatin after HU-induced replication stress,²¹⁸ which may suggest possible crosstalk between FANCD2 and Poln in facilitating CFS replication. Moreover, a previous study demonstrated the role of Rev3, the catalytic subunit of Pol ζ , in preventing CFS instability, suggesting that Rev3-mediated DNA synthesis is activated during G2-M phase to allow completion of replication at CFSs before chromosome segregation.¹⁹⁴ On the other hand, a recent study by Gallina et al. demonstrated that mitotic DNA synthesis is independent of DNA Pol η and TLS.²¹⁹ Specifically, this study showed that unscheduled DNA synthesis in mitosis is independent of Rev1 and ubiquitinated PCNA in DT40 chicken cells and that Pol η does not colocalize with either TopBP1 or FANCD2 foci in mitotic cells, indicating that nucleotide incorporation in mitosis is not due to the TLS pathway. Taken together, these studies suggest a putative but unclear role for TLS polymerases in the mechanism that leads to resolution of incomplete DNA replication that persists in late G2 to mitosis. Recent studies suggest that specialized polymerases, apart from their role in bypassing damaged DNA templates, may participate in replication across non canonical DNA structures and difficult to replicate loci.²²⁰ Interestingly, in yeast, Pol31 (POLD2) and Pol32 (POLD3) accessory subunits of Pol δ have been shown to copurify with the Rev3 and Rev7 subunits of Pol² to form a 4-subunit Pol ζ complex, leading to the hypothesis that the Pol ζ holoenzyme may replace Pol δ at replication blocking lesions or perform TLS or other PCNA-dependent cellular functions.²²¹⁻²²³ Moreover, the TLS polymerases pol and Rev1 have been recently shown to promote template switching during MMBIR, leading to genome rearrangements.²²⁴ Therefore, it is tempting to speculate that specialized polymerases may promote replication or replication-associated repair pathways at challenging loci, which can both prevent or promote genome instability.

It has been proposed that the appearance of gaps and breaks on mitotic chromosomes (CFS expression) is the cytogenetic manifestation of mitotic repair synthesis taking place at these sites, to limit chromosome non-disjunction and mis-segregation.²² However, inhibition of mitotic DNA synthesis may not always be associated with a decreased CFS expression.^{23, 194} Indeed, TopBP1 deficiency impairs mitotic synthesis but is associated with an increased CFS expression.²³ Moreover, mitotic synthesis and CFS expression are not systematically associated with the rescue of anaphase bridges. For instance, ATR- or FA-deficient cells display both an increased CFS expression and mitotic synthesis, together with an increased frequency of anaphase bridges.^{12,161,168,184,195,225} In BLM-deficient cells, the downregulated expression of cytidine deaminase (CDA, an enzyme involved in the pyrimidine salvage pathway) leads to an increase in the dCTP pool and reduced PARP-1 activity, with a consequent increase in mitotic DNA synthesis and UFB frequency.¹⁹⁶ Therefore, delayed DNA synthesis may not be sufficient to complete replication, leaving specific loci incompletely replicated. The pool of nucleotides is regulated during the cell cycle; therefore, unscheduled DNA synthesis may be inefficient or inaccurate.²²⁶ Alternatively, rescue of under-replicated DNA during mitosis may result in an excess of replication or repair intermediates that overwhelm the resolution pathways. Therefore, we favor the view that CFSs represent replication termination zones where processing of replication or repair intermediates is still ongoing or incomplete, preventing the proper resolution of topological constraints and chromatin organization.

Consequences of failed rescue of replicative stress in mitosis

Absence of rescue of replicative DNA damage in mitosis can have detrimental consequences for cells, as it may lead to tumorigenesis. However, healthy cells are able to prevent carcinogenesis by activating the p53 pathway that leads to apoptotic cell death.²²⁷ Alternatively, in primary cells, for example, replication stress can induce a response that leads to proliferation and cell growth arrest, a phenomenon called cellular senescence.²²⁸ Cell death in mitosis and formation of 53BP1 nuclear bodies are the primary mechanisms that protect cells with persisting damage or under-replicated DNA in mitosis from becoming carcino-genic.^{17, 229} However, despite the efficiency of these mechanisms, cells can be defective in one of these pathways and, therefore, become micronucleated or aneuploid, leading to tumorigenesis.

Mitotic catastrophe

Cell death in mitosis, also known as mitotic catastrophe, is the result of failure to complete mitosis.²²⁹ It usually occurs as a consequence of serious problems of nondisjunction or after centrosome overduplication and consequent entry into mitosis

with multiple spindle poles.²³⁰ Although there are several studies linking apoptosis to mitotic catastrophe, it is still unclear whether mitotic catastrophe is an apoptotic mechanism.²³¹ However, mitotic catastrophe remains a cell death mechanism that can eliminate cells with persistent replicative DNA damage and prevent carcinogenesis.

53BP1 bodies

53BP1 is a DNA repair marker that colocalizes with γ H2AX at DSBs. It has been recently shown that 53BP1 makes foci at persisting DNA lesions induced by replication stress.^{17, 18} Specifically, 53BP1 forms large nuclear structures called "bodies" in the subsequent G1-phase of the cell cycle. These bodies preferentially associate with CFSs and are largely induced in the absence of BLM.¹⁷ The biologic function of 53BP1 bodies could be to shield DNA lesions that remain unrepaired during the transition from G2 to mitosis, so that they are efficiently repaired in the next cell cycle.¹⁷ Recently, it has been shown that 53BP1 bodies contain ssDNA marked by RPA and increase following MCM depletion, due to the presence of large replicons devoid of origins.²³² This finding is consistent with the fact that 53BP1 bodies occur due to under-replicated DNA persisting in mitosis and are enriched at CFSs following replication stress. 53BP1 bodies are also stained by DSB markers, which can result from breakage of under-replicated DNA or unresolved DNA structures at the end of mitosis.^{20,21,233} 53BP1 bodies may also be associated with other types of DNA or chromatin alterations that are transmitted in G1, which depend on TopBP1 for their resolution in mitosis.²³ There are 2 most likely functions for 53BP1 in the cell cycle following DNA damage. The first is promotion of Non-Homologous End Joining (NHEJ) that occurs in G1,²³⁴ which could, however, be errorprone and promote inappropriate joining of DNA ends, leading to chromosomal rearrangements.²³⁵ The second possibility is that it shields the damaged sites from excessive resection and aberrant repair in G1 and protects them until entry into Sphase, when they can be repaired by HR-mediated mechanisms.¹⁷ The latter possibility is supported by the fact that 53BP1 bodies stay in the nucleus up until entry of the cell into the subsequent S-phase. 53BP1 may allow for repair of some lesions, while protecting complex DNA lesions from further damage or error-prone repair and, therefore, prevent carcinogenesis. Further work would be required to know whether these large nuclear bodies mark clustered DNA lesions or chromatin domains and to have a better understanding of the function of 53BP1 in the cell cycle following replication stress.

Non-disjunction and aneuploidy

Failure to recover from replication stress and to resolve joint molecules that persist in mitosis can also result in chromosome non-disjunction and mis-segregation, leading to gain or loss of chromosome fragments or whole chromosomes.¹² The latter situation, known as aneuploidy, is a common cancer trigger and may explain why patients with mutations in genes regulating replication stress are often susceptible to cancer.^{14,236} Interestingly, it has been shown that supernumerary chromosomes can generate additional replication stress, thus precipitating

genomic instability.²³⁶ In addition, aneuploidy can induce changes in gene expression and proteotoxic stress, leading to deregulation of cellular functions and homeostasis.²³⁷⁻²³⁹

Micronuclei

A frequent outcome of the absence of rescue of replicative stress in mitosis is the formation of small chromatin masses called micronuclei.¹² These small nuclear fragments, also known as Howell-Jolly bodies, represent lagging chromosomes or chromosome fragments that were unable to properly segregate with the rest of the genome but were efficiently nucleated after the end of mitosis.²⁴⁰ Replication of these micronuclei in the subsequent S-phase is abnormal and may lead to further chromosomal aberrations. The micronuclei can eventually fuse with the main nucleus, leading to large chromosomal abnormalities, or become shattered into small pieces, a phenomenon called chromothripsis.²⁴¹ In both cases, the cells accumulate serious irreversible genome modifications, such as chromosome deletions, triplications, inversions and translocations, which may subsequently lead to cancer.

Cytokinesis failure

Another consequence of replication stress and failure to resolve chromosome entanglements is impairment of cytokinesis. Indeed, persistent anaphase bridges and UFBs have been shown to inhibit abscission and result in binucleated cells.^{23,149,161} The presence of lagging chromosomes or chromatin bridges in telophase has been shown to activate a pathway called NoCut in yeast and an AuroraB-dependent abscission checkpoint in higher eukaryotes to delay cytokinesis and inhibit abscission, allowing the cell to segregate all the genetic material.²⁴²⁻²⁴⁴ Defective activation of this pathway can lead to breakage of chromosomes trapped in the spindle midzone or to furrow regression and tetraploidy. Conversely, delay or failure to resolve anaphase bridges and persistent activation of this pathway may impair abscission. Anaphase bridges and lagging chromosomes following replication stress can also lead to chromosome breakage and aneuploidy¹² and may be the cause of numerical and structural chromosomal rearrangements in tumor cells.¹⁴ A recent work has shown that chromatin bridges induced by replication stress are able to activate the NoCut pathway, leading to cytokinesis delay, while lagging chromosomes or anaphase bridges resulting from dicentric chromosomes do not activate this pathway, and thus, lead to aneuploidy and chromosome breakage.²⁴⁵ This may explain the different fates of anaphase bridges and lagging chromosomes arising from different causes, and it suggests that structural and numerical chromosome aberrations after replication stress may be the result of dicentric chromosomes or chromosome structures that are severed during anaphase or cytokinesis and/or do not activate this checkpoint.235,246-248 Indeed, ATR and chk1 have been shown to link replication stress with the AuroraB pathway and to regulate the timing of abscission at the midbody stage.²⁴⁹ Interestingly, ATR-deficient cells undergoing mitosis with under-replicated DNA show segregation defects and cytokinesis failure, which can be mitigated by partial inhibition of Cdk1 activity.¹⁶⁸ Therefore, a tight coordination

between under-replicated DNA processing and cytokinesis may be crucial for timely resolution of chromosome entanglements and abscission.

Epigenetic instability

Another outcome of replication stress and DNA damage is perturbation of histone recycling and restoration of chromatin structure, which can affect epigenetic maintenance and cell function.^{97,250-254} For example, replication fork blockage at Grich genomic sequences has been associated with a biased incorporation of H4-acetylated histones and loss of repressive chromatin marks.²⁵⁵ Conversely, uncoupling of DNA replication with new histone deposition has also been shown to alter predeposition marks on new histones and induce heterochromatinization and gene silencing.²⁵⁶ Likewise, trinucleotide repeat expansion was shown to mediate gene silencing.²⁵⁷ Moreover, inhibition of DNA synthesis may also alter DNA methylation.²⁵⁸ Persistence of under-replicated DNA in mitosis may therefore interfere with normal chromatin reassembly and propagation of the epigenetic information. Indeed, UFBs are largely devoid of histones and therefore, need chromatin structure and epigenetic information to be re-established in the next cell cycle. How the cells cope with epigenome maintenance after persistent replication stress in mitosis is largely unknown. Interestingly, recent studies have shown that Drosophila male germline stem cells that divide by asymmetric cell division differentially distribute old and new histones, and selectively segregate the parental histones into the stem cell and the newly synthesized histones into the differentiating daughter cell.²⁵⁹ One could speculate that differential histone incorporation following replication stress or DNA damage may allow discrimination between daughter cells and determine cell fate.²⁵²

The role of mitotic replication stress in human disease

The most common human disease associated with defective rescue of replication stress is cancer.²⁶⁰ The inability to repair fragility at CFSs or anaphase bridges persisting into telophase leads to chromosome mis-segregation, micronuclei formation and aneuploidy, which are often present in cancer cells. Cells with micronuclei or an abnormal number of chromosomes become carcinogenic, either by losing the expression of tumor suppressors or by activating the expression of oncogenes. These transformed cells then lose their proliferation control and create tumors that eventually lead to organ failure.²

A common characteristic of many cancers is the genomic instability observed at CFSs. CFS breakage may induce recombinogenic events, viral integrations, and chromosomal rearrangements.¹¹⁶ Indeed, recent analyses of cancer genomes have revealed that CFSs are involved in the majority of recurrent chromosomal deletions and translocations in cancer.²⁶¹⁻²⁶³ Importantly, CFSs represent the preferential targets of oncogene-induced replication stress and are involved in the formation of DSBs that contribute to genomic instability in the earliest stages of tumor development.⁷⁷ However, the contribution of CFSs to the tumorigenic process is still under debate.²⁶⁴ Molecular characterization of CFSs has shown that many of them map within or in proximity to cancer-associated genes,

which are aberrantly expressed in several tumors.^{265,266} One of the most well-studied CFSs, FRA3B, which shows a high frequency of breakage in lymphocytes and is frequently abnormal in epithelial tumors,^{263,267} is located within the Fragile Histidine Triad (FHIT) gene. The protein encoded by FHIT is involved in the DNA damage response, nucleotide metabolism and apoptosis.^{116,268} Loss of FHIT expression induces replication stress and accumulation of DNA damage, leading to genomic instability and promotion of tumorigenesis.²⁶⁸ Other CFSs that overlap with known tumor-suppressor genes are FRA16D, located within a gene encoding for the multifunctional enzyme WW-domain containing oxidoreductase (WWOX), and FRA6E, located within the PARK2 gene encoding the E3 ubiquitin ligase that is mutated in Parkinson disease, which has been shown to regulate cyclin turnover.²⁶⁹⁻²⁷² Breakage at these sites, resulting in loss-of-function of these tumor-suppressor genes, provides a possible explanation of how CFS instability can contribute to cancer initiation and progression. In addition, CFS expression can promote the amplification of oncogenes located in their proximity via breakage-fusion-breakage mechanisms, as described, for example, for MET at FRA7G or PIP at FRA7L²⁷³⁻²⁷⁵

Apart from cancer, many known syndromes are associated with mutations in genes involved in the rescue of mitotic replication stress.² Seckel syndrome, for example, a developmental disease characterized by dwarfism, microcephaly and mental deficiencies, is induced by mutations in ATR or ATRIP. Fanconi anemia is another example of such a disease; individuals with mutations in FA genes are characterized by a wide range of symptoms from skeletal and developmental defects to cancer predisposition and progressive bone marrow failure.^{276,277} Indeed, FA cells show a high frequency of abnormal chromosome structures that may occur as a result of persistent replication stress during mitosis. FA patients display chromosomal aberrations at CFS loci.²⁷⁸⁻²⁸¹ Importantly, persistent anaphase bridges have been observed in haematopoietic cells of FA mice, even in unperturbed conditions and are associated with cytokinesis failure and increased apoptotic cell death,¹⁶¹ suggesting that endogenous replication stress or unresolved DNA damage that persists in mitosis may contribute to bone marrow failure and account for the exacerbated p53/p21 activation observed in FA.¹⁷¹ Recently, the FA pathway has also been shown to counteract physiologic stress during megakaryopoiesis, preventing CFS instability and cell division abnormalities associated with defective megakaryocyte differentiation and thrombocytopenia of FA mice.²⁸² Finally, a variant form of xeroderma pigmentosum (XPV) is a cancer-prone disease that is caused by mutations in the gene coding for the TLS polymerase Pol_{η} , a protein shown to have a role in DNA synthesis at CFSs.⁶

Deficiency in BLM protein leads to a disease that has similar symptoms to FA but is also characterized by immunodeficiency and premature aging.²⁸³ Aging is prematurely induced in syndromes characterized by mutations in RecQ DNA helicases, such as the Werner (WRN) helicase (Werner's syndrome) or the RecQL4 helicase (Rothmund-Thomson syndrome)[283]. Apart from BLM, WRN has also been shown to have a functional role in preventing replication stress by regulating CFS stability.²⁸⁴ These syndromes indicate that the inability to

properly and timely resolve replication challenges at CFS, telomeres and/or other difficult-to-replicate loci may affect overall cellular morphology and homeostasis and eventually lead to aging.

Interestingly, replication stress may also be associated with neurodevelopmental and neurodegenerative disorders.¹²¹ Epilepsy, schizophrenia and autism are neurologic syndromes associated with genomic CNVs, which might occur as a result of defective repair at CFSs. Indeed, a recent study has shown that long genes with neural function are hotspots of recurrent DSB clusters (RDCs) in neuronal stem cells.²⁸⁵ Most of these RDCs were induced by low-dose APH treatment and mapped within long, transcribed and late-replicating genes associated to CFSs. It would be important to better understand the link between the expression of these genes and their fragility, and to determine whether somatic CNVs in these genes can modulate neuronal function and plasticity. Moreover, mutations in the gene encoding for Senataxin (SETX), a protein involved in resolving collisions between transcription and replication and, therefore, preventing R-loop formation, lead to various neurodegenerative diseases, such as amyotrophic lateral sclerosis 4 and ataxia-ocular apraxia 2.106,286 The molecular link between neurologic diseases and replication stress may lie in the fact that many of the genes involved in brain development are long and are therefore more susceptible to collisions between transcription and replication,127 transcription-associated DNA damage, or replication stress-induced segregation defects and aneuploidy.287

Concluding remarks

Replication stress is one of the most important molecular triggers of carcinogenesis. Our knowledge of the DNA damage response to decelerated or aborted DNA replication has dramatically expanded during the last 2 decades. Although the replication stress response is largely constrained within S-phase, with the help of the ATR/Chk1-induced intra S-phase checkpoint, recent studies have shown that endogenous or mild replication stress can lead to the persistence of under-replicated or unresolved DNA structures in mitosis. This persistence can have detrimental consequences for the cell, as it may lead to chromosome nondisjunction and other aberrant mitotic events that can limit cell survival or alter normal cellular function and organismal development. In addition, it could also drive genetic and epigenetic instability, promoting cancer initiation and progression. We have just started to identify the mechanisms by which the cell is able to resolve this persistent replication stress in mitosis and some of the key factors and pathways involved (Fig. 1). Although the role of these proteins has been partially characterized, we still do not know how chromatin binding or the activity of these proteins is regulated, the intermediates they act on, or how these factors cooperate to resolve replication stress before the end of mitosis. We also expect that other factors that will contribute to our understanding of MRRS await identification and may provide important clues to the mechanisms involved in the development of disease, including cancer. A major challenge of future studies will be to understand how transcription and RNA metabolism regulators



Figure 1. Schematic diagram summarizing the cellular response to under-replicated DNA that persists in mitosis. FANCD2 and TopBP1 bind at sites of incomplete DNA replication during late G2/early prophase. Then, with the help of SLX4, the endonucleases MUS81 and ERCC1 bind at these sites and mediate nucleolytic cleavage of replication intermediates. This allows repair synthesis to occur to complete DNA replication and/or resolution of joint molecule intermediates, promoting proper chromosome segregation. In the absence of FANCD2, TopBP1, SLX4, MUS81 or ERCC1, a bulky or ultra-fine anaphase bridge (UFB) may form from interlinked or under-replicated DNA. The UFB may be resolved before completion of anaphase with the help of FANCD2, TopBP1, PICH, Rif1 and BLM, or transition into 53BP1 bodies in the daughter cells. However, unresolved joint molecule intermediates, persistent UFBs and bulky chromatin bridges, lead to chromosome disjunction, segregation defects and cell division abnormalities, which result in mitotic catastrophe, binucleation, aneuploidy or formation of micronuclei. Finally, nucleolytic cleavage and aberrant repair of under-replicated DNA in prophase may also lead to chromosomal deletions, amplifications or rearrangements that have detrimental consequences for the cell.

interact with replication and repair machineries to prevent or resolve potential conflicts between these metabolic processes and how they are coordinated with chromatin modifications and chromosome architecture during mitosis to ensure accurate transmission of the genetic and epigenetic information to daughter cells.

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No potential conflicts of interest were disclosed.

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