The role of chromatin at transcription-replication conflicts as a genome safeguard

Aleix Bayona-Feliu[1,2] and Andrés Aguilera[1,2,] *

[1] *Centro Andaluz de Biología Molecular y Medicina Regenerativa CABIMER, Universidad de Sevilla-CSIC, Sevilla 41092, Spain*

[2] *Departamento de Genética, Facultad de Biología, Universidad de Sevilla, Seville 41012, Spain*

* *Corresponding author*. *E-mail:* aguilo@us.es

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ABSTRACT

DNA replication ensures the correct copying of the genome and the faithful transfer of the genetic information to the offspring. However, obstacles to replication fork (RF) progression cause RF stalling and compromise efficient genome duplication. Since replication uses the same DNA template as transcription, both transcription and replication must be coordinated to prevent Transcription-Replication Conflicts (TRCs) that could stall RF progression. Several factors contribute to limit the occurrence of such conflicts and their harmful impact on genome integrity. Increasing evidence indicates that chromatin homeostasis plays a key role in the cellular response to TRCs as well as in the preservation of genome integrity. Indeed, chromatin regulating enzymes are frequently mutated in cancer cells, a common characteristic of which is genome instability. Therefore, understanding the role of chromatin in TRC occurrence and resolution may help identify the molecular mechanism by which chromatin protects genome integrity, and the causes and physiological relevance of the high mutation rates of chromatin regulating factors in cancer. Here we review the current knowledge in the field, as well as the perspectives and future applications.

Abstract: 178 words

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Introduction

Genome stability ensures cell viability, even though certain variability is required for species adaptation and survival. DNA is constantly subjected to either exogenous or endogenous damaging agents that might result in DNA damage and eventually genome instability if not properly addressed.

In eukaryotes, DNA replication is bidirectional and initiates at multiple origins to produce a new copy of the whole genome. During this process, replication forks (RFs) have to deal with multiple obstacles to their progression that may compromise accurate genome duplication (1,2). Obstacles include DNA-bound proteins, DNA damage, topological stress, chromatin structure or transcription. Replication and transcription use the same DNA substrate, and several reports have shown the potential of transcription to stall DNA replication, thus compromising genome integrity (3–5). Interestingly, hazardous RF stalling may be further enhanced by the formation of transcription-associated obstacles, including non-B DNA structures. Consequently, cells have developed several mechanisms to prevent and solve transcription-replication conflicts (TRCs).

TRCs are actively prevented via different pathways that avoid the formation of transcription-associated obstacles (2). Nevertheless, when occurring, transcription-mediated RF stalling may be solved via a coordinated response involving checkpoint activation, RF stabilization and obstacle removal. Thus, cancer-associated genes as BRCA1/2 and Fanconi Anemia factors have been shown to play a key role during this process (6–9). Recently, however, chromatin remodeling has also emerged as a major player in this response. Indeed, the SWItch/Sucrose Non-Fermentable (SWI/SNF), INOsitol requiring 80 (INO80) or FAcilitates Chromatin Transcription (FACT) chromatin remodeling complexes counteract TRC occurrence (10–13). Interestingly, SWI/SNF components, in particular its main ATPase activity SMARCA4, best known as Brahma-Related Gene 1 (BRG1), are frequently altered in cancer, reaching mutation frequencies only surpassed by Tumor Protein P53 (TP53) (14).

Increasing evidence suggests that genes highly mutated in cancer play key roles during tumorigenesis, which may pose an important endogenous instigator of genome instability. Therefore, understanding the underlying mechanisms through which cells prevent TRCs from resulting in genome instability-associated diseases is essential to achieve new therapeutic opportunities against the disease. In this review, we try to gather our current knowledge on how the chromatin network impacts on TRC occurrence and resolution to preserve genome stability. Other reviews have been published on the causes and consequences of TRCs (1,15–17).

Transcription as a source of replication stress

The essential fine-tuned process of transcription uses as template the DNA, which has to be replicated at each cell cycle. Consequently, it is possible that conflict scenarios between transcription and replication raise during S phase at regions in which both processes occur concomitantly. Indeed, numerous reports show that transcription is a potential source of RF stalling and DNA replication stress (1). Thus, the transcription machinery itself and transcription-induced structures such as DNA supercoiling, non-B DNA structures (DNA-RNA hybrids; G4s), DNA damage or closed chromatin states may pose an obstacle to RF progression (Figure 1).

The transcription machinery

Similar to tightly-bound proteins, the transcription machinery may become a roadblock to RF progression. Indeed, yeast mutants undergoing RNA Polymerase II (RNAPII) retention at chromatin result in DNA replication stress (18) and RNAPII has been shown to be released from chromatin after replication stress thru a process involving INO80C and the RNA processing PAF complex in yeast (11). Ongoing RNAPs may also pause, arrest and/or backtrack when facing DNA damage, from which cells take advantage by promoting transcription-coupled repair (TCR) (19). In human cells, the RECQL5 helicase of the RecQ family has been shown to prevent RNAPII backtracking and promote transcription elongation, thus avoiding TRCs (20,21), and supporting the view that backtracked RNAPs may be important obstacles to advancing RFs. Transcription termination factors (TTFs) also prevent RNAPs from becoming a barrier to replication. Thus, yeast transcription termination mutants affecting RNA 5’ and 3’ end processing factors Rna14 and Rna15, Fip1, Usp6/Hrp1, the 5'-3' Exoribonuclease 2 Xrn2 or the RNA helicase Sen1 (ortholog of human Senataxin) present inefficient termination and transcription-dependent replication hampering (22–24). Altogether, the data indicate that cells have developed several mechanisms acting at different steps during the transcription process to avoid that the transcription machinery becomes a barrier to RF progression.

Transcriptional topological stress

Positive and negative supercoiling accumulate ahead and behind RNAP, respectively, during transcription elongation (25). While positive supercoiling limits further unwinding of DNA, negative supercoiling can result in DNA alterations making it prone to open and form non-B DNA structures. On the other hand, positive supercoiling accumulated between RNAP and an RF advancing in head-on orientation may stall RF progression without the need of a physical collision between the transcription and replication

machineries (Figure 1). Nevertheless, topoisomerases are capable of dealing with transcription-induced supercoiled DNA structures ensuring they do not compromise genome integrity (26–29). Therefore, enzymatic activities acting on supercoiled DNA such as topoisomerases plus their interacting partners might play an important role in preventing transcription-associated genome instability.

Co-transcriptional DNA-RNA hybrids

Current evidence indicates that nascent transcripts can hybridize with the template DNA resulting in the formation of a DNA-RNA hybrid, which may further interfere with the DNA replication process (1) (Figure 1). Hybrids may form during transcription in the form of an R-loop containing in addition the displaced ssDNA identical to the RNA moiety of the hybrid. R-loops can also form at the vicinity of double strand breaks (DSBs) and evidence has also been provided that TRCs may lead to R loops (30,31), In addition, the cell cycle phase is a major determinant of the type of molecular event resulting in an R-loop (32,33). R-loops may occur naturally with a physiological role, as in the S regions of the Immunoglobulin genes. Nevertheless, unscheduled R-loop formation compromises genome integrity (2). Current data supports the view that persistent unscheduled R-loop accumulation results in DNA damage mainly as a consequence of replication blockage, even though other mechanisms, such as the action of nucleotide excision repair (NER) nucleases XPG or XPF can also cause such DNA breaks (34). Consequently, cells have developed mechanisms to prevent unscheduled R-loop accumulation (Figure 1). These strategies include proper assembly of the messenger ribonucleoprotein (mRNP), activities to resolve the R-loops as DNA-RNA helicases or ribonuclease H (RNH), which degrades the RNA moiety of the hybrids, and the DNA Damage Response (DDR), as recently reviewed (35).

A role of chromatin in the coordination of transcription and replication

The involvement of chromatin in regulation of gene expression has been largely explored and several epigenetic mechanisms have been described to help regulate transcription (36). In the last years, growing evidence indicates that chromatin homeostasis must also be properly preserved to prevent transcription-associated genomic instability. DNA methylation, histone post-translational modifications, ATP-dependent chromatin remodeling and even RNA modifications have been described to influence TRC-mediated DNA damage (Figure 2).

DNA methylation

Initial genome-wide analysis of DNA-RNA hybrids unveiled that they are enhanced at CpG island (CGI)-promoters and its occurrence correlates with unmethylated states of CGIs. Indeed, R-loops protect CGI from the methyltransferase 3B1 (DNMT3B1) activity, a major *de novo* DNMT in early development (37) (Figure 2a). Interestingly, low R-loop levels lead to high DNA methylation and gene silencing in Amyotrophic Lateral Sclerosis (ALS) 4 patient cells, as suggested by the observation that DNMTs bind much more efficiently to dsDNA than to DNA-RNA hybrid-prone sequences (38). A different study also points to a role for the GADD45 factor in this process (39). Notably, GADD45A was found to bind R-loop-prone regions next to promoters and trigger DNA demethylation thru recruitment of Ten-Eleven Translocation 1 (TET1) (Figure 2a), suggesting that GADD45A might work as an epigenetic reader that induces promoter CGI demethylation in response to R-loop formation. Thus, R-loops formed at CGI-promoters seems to favor gene transcription by reducing DNMTs' affinity to genomic DNA containing DNA-RNA hybrids thus leading to promoter demethylation.

Histones and their post-translational modifications

Physiological R-loops occurring at promoter regions have been found enriched in histone post-translational modifications (PTMs) associated with active transcription (40). In particular, high levels of histone H3 lysine 4 di/trimethylation (H3K4me2/me3), lysine 9/27 acetylation (H3K9/K27ac) and of certain H3.3 histone variants, but low histone H3 lysine 9 trimethylation (H3K9me3) are observed close to TSSs at R-loop-prone promoters. Instead, histone H3 lysine 4 mono-methylation (H3K4me1) and lysine 36 methylation (H3K36me) are enhanced at the R-loop-accumulating sites of such promoters. On the other hand, R-loops emerging at transcription termination sequences show an association with increased H3K4me1 levels. Interestingly, H3K4me has been shown to play a key role ensuring S-phase checkpoint activity and reliable DNA duplication under replication stress as seen in highly transcribed yeast genes (41). Histone H3 lysine 9 dimethylation (H3K9me2) has also been reported to promote efficient transcription termination in mammalian protein-coding genes prone to R-loop formation at transcription termination sites (TTSs) (42).

Unscheduled R-loops have been associated with increases in repressive epigenetic marks such as histone H3 serine 10 phosphorylation (H3S10P) and H3K9me2/3 (Figure 2b). R-loop-dependent H3S10P accumulation was found in R-loop-prone mutants in yeast, *C. elegans* and human cells, suggesting the effect is conserved among species (43). Further investigation in yeast unveiled that such a

modification was causative of the observed genomic instability, as yeast mutants impaired in histone H3S10P formation result in R-loop accumulation not associated with increased DNA damage (44). Interestingly, Aurora Kinase A (AURKA) was recently revealed to mediate R-loop-dependent H3S10P deposition during S phase and its inhibition results in TRCs and checkpoint activation in MYCN-amplified neuroblastoma cells (45). Thus, H3S10P and AURKA, might play key roles preventing transcription-dependent RF stalling and its deleterious consequences in S phase. Aberrant R-loops have also been reported in triplet-repeat expansions, a feature of Friedrich's ataxia and Fragile X syndrome that are associated with ectopic repressive H3K9me2/3 that impedes RNAPII progression and results in gene silencing (46).

Linker histone H1, which has been related to chromatin compaction and heterochromatin, prevents R-loop-mediated DNA damage as well (Figure 2b). Histone H1 depletion in *Drosophila* results in R-loop-dependent genome instability in heterochromatin (47), and accumulation of transcription-dependent stalled forks and DNA damage are observed in histone H1 triple knock-out (TKO) human cells (48). Therefore, linker histones might help coordinate transcription and DNA replication to prevent transcription-induced DNA damage.

Chromatin modifiers

Genome-wide analyses have revealed that components of COMPASS (RBBP5), PAF1C (PAF1), SIN3 complex (SIN3A; SAP30; HDAC2), p300 acetyltransferase, EZH2 methyltransferase and KDM4A and PHF8 histone demethylases are found at high frequency at R-loop-prone promoters, and higher abundance of PAF1, CTCF and cohesin components ZNF143 and RAD21 are detected at R-loop-prone TTSs (40).

However, deficiencies in several chromatin-modifying activities have been observed to promote R-loop-dependent genome instability. Regulators of histone acetylation/deacetylation might play a key role in this process, as several reports have connected deficiencies in such activities with unscheduled R-loop formation and DNA damage. Thus, depletion of Sin3A histone deacetylase (HDAC) complex factors (SIN3; SAP130) as well as histone deacetylation inhibition produced by trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA) results in an accumulation of R-loops and R-loop-dependent DNA damage in human cells (49) (Figure 2c). Similarly, R-loop-dependent genome instability phenotypes are also induced by deficiencies in sirtuins (NAD+-dependent deacetylases). R-loop-dependent DSBs arise in *hst3* and *hst4* yeast mutants of the hSIRT6 homologs (50) and in SIRT7-deficient human cells (51). In human cells the HDAC inhibitor romidepsin also causes R-loop-mediated ssDNA breaks (52). On the other hand, the Tip60-400 histone acetyltransferase complex

associates with genes harboring promoter-proximal R-loops and influence genome-wide occupancy of polycomb repressor complex (PRC)-2 (PRC2) histone methyltransferase (53). Deficiency of Bromodomain-containing protein 4 (BRD4), a reader that recognizes and binds acetylated histones, was also shown to cause an increase in R-loops, TRCs and DNA damage, consistent with a major role for histone acetylation state on R-loop homeostasis (54).

Chromatin-modifying enzymes regulating other epigenetic marks different from histone acetylation participate either in this process. PRC1 was reported to act in parallel with Mdm2, a chromatin modifier modulating PRC-driven histone modifications, suppressing R-loop formation and promoting productive DNA replication via a direct impact on histone H2A lysine 118/119 (K118/K119) ubiquitination (55). Indeed, R-loops drive Polycomb repression at a subgroup of developmental genes (56) (Figure 2c). At these genes, decreased PRC1 and PRC2 abundance, RNAPII activation and productive transcript elongation were observed upon R-loop removal. Furthermore, a connection between R-loop formation and Euchromatic Histone Lysine Methyltransferase 2 (EHMT2), also known as G9a, has also been described at TTSs (42) (Figure 2c). At these sites, R-loop formation was suggested to drive G9a recruitment and results in histone H3K9me2, promoting RNAPII pausing and facilitating termination.

Histone chaperones

In agreement with a major impact of the content of histones and their PTMs, histone turnover also mediates transcription-associated RF stalling. The histone chaperone FACT was observed to prevent transcription-mediated genome instability, since its deficiency results in transcription-associated DNA damage and RF progression impairment in yeast and human cells (13) (Figure 2d). The observation that the MCM2-7 helicase dissociates from chromatin in FACT-deficient cells causing loss of ssDNA-RPA binding and checkpoint activation (57) may be behind the replication deficiency, even though it needs experimental evidence.

FACT and Chromatin Assembly Factor-1 (CAF1) histone chaperones have been described to be specifically recruited at transcribing loci to facilitate RF progression (58) (Figure 2d). Notably, CAF-1 depletion was shown to slow down DNA replication and promote CHK1 phosphorylation at serine 317, a mark associated with DNA replication stress (59). Similarly, the Anti-Silencing Function 1 (ASF1) factor has also been implicated in promoting RF progression by driving recycling of H3-H4 tetramers in conjunction with CAF-1 (60). Indeed, ASF1 deficiency promotes replication-dependent genome instability and sensitizes cells to replication stress-

inducing compounds (61,62). The results suggest that histone turnover must be properly regulated to ensure efficient RF progression, especially at regions enriched in transcription-associated obstacles.

ATP-dependent chromatin remodeling

Nucleosome positioning on chromatin depends directly on the coordinated action of histone chaperons and ATP-dependent chromatin remodelers. Consistent with the idea of a major contribution of chromatin to the resolution of TRCs, remodeling activities are also emerging as required to prevent transcription-associated genome instability. Indeed, members of different chromatin remodeling families (SWI/SNF, INO80, ISWI) have been shown to protect against transcription-dependent DNA damage.

The SWI/SNF complex, the ATP-dependent chromatin remodeling complex most frequently altered in cancer (63), has recently being shown to control TRCs (10). Depletion of BRG1, the main SWI/SNF ATPase, is epistatic to FANCD2 deficiency in its capacity to help solve TRCs, especially those occurring in a head-on orientation (Figure 2e). Consistently, BRG1 co-localizes with DNA replication factors and promote RF progression. In addition, AT-Rich Interaction Domain 1A (ARID1A) and Polybromo 1 (PBRM1), members of the canonical BRG1-associated factor (cBAF) and polybromo BRG1-associated factor (PBAF) SWI/SNF complex subtypes, respectively, were also reported to protect from transcription-associated DNA damage. Similalry, ARID1A and PBRM1 deficiencies also induce R-loop-dependent DNA damage. Additionally, a recently observed connection between ARID1A and topoisomerase IIa (TOP2A) at TRCs (64) and high levels of replication stress, micronuclei and R-loops in PBRM1-deficient human cells (65), further supports the involvement of SWI/SNF at TRCs. Interestingly, another member of the SWI/SNF family, Alpha Thalassemia/Mental Retardation Syndrome X-Linked (ATRX), suppress R-loop formation in telomeric repeats (66). All these factors present high mutation frequencies in malignant cells, suggesting a possible relation with the high mutation rates observed in cancer.

INO80C has been implicated in RNAPII release from chromatin together with the PAF RNA processing complex thus limiting TRCs in budding yeast (11). Interestingly, INO80 prevents R-loop-dependent DNA damage in prostate cancer PC3 human cells (12) (Figure 2e), and R-loops promote recruitment of INO80 protein to chromatin. In agreement, yeast Ino80, the ATPase component of the INO80 complex, was reported to function in parallel with Isw2, the catalytic component of the ISW2 complex, promoting RF progression (67). Transcription-dependent hyper-recombination was shown to increase also in yeast cells lacking Isw1, the catalytic subunit of the yeast ISW1 complex (68). Similar mechanisms might also exist in human

cells as the human Isw1 orthologue SMARCA5, best known as SNF2H, the core subunit in several ISWI-family complexes in human cells, has also been reported to be recruited to DNA breaks and prevent genome instability (69).

RNA modification and editing

Novel regulatory mechanisms involving RNA modification and editing have been reported as suppressors of unscheduled R-loop formation. Methylation of the N6 position of adenosine (m6A) of RNA has been described to promote co-transcriptional R-loops at TTSs and, thus, prevent RNAPII readthrough and favor termination (70). m6A methyltransferase METTL3 depletion results in diminished R-loops at TTSs and aberrant termination in m6A+ genes. Interestingly, METTL3 has been reported to methylate m6A in DNA damage-associated RNAs, thus inducing recruitment of the m6A reader YTHDC1 (71), and that METTL3-m6A-YTHDC1 joint action regulates DNA-RNA hybrid accumulation at DSBs. Similarly, the "tonicity-responsive enhancer binding protein" (TonEBP) is able to recognize R-loops and recruit METTL3 and RNase H1 to promote R-loop suppression (72) (Figure 2f).

m6A RNA modification was also identified in DNA-RNA hybrids from human pluripotent stem cells (73). Such a modification was found to regulate R-loop accumulation through the cell cycle by promoting m6A+ RNA degradation in dividing cells, a process involving the m6A reader YTHDF2 (Figure 2f). In *Arabidopsis*, R-loops promote chromatin silencing via a mechanism involving also m6A RNA modification at the FLC gene (74).

In addition to m6A, methylation of N5 position of cytosine (m5C) in mRNAs promoted by methyltransferase TRDMT1 also occurs at DSBs (75) (Figure 2f). Interestingly, m5C increases the affinity of RAD52 recombination factor to DNA-RNA hybrids, suggesting a direct involvement of the m5C modification in the DDR.

Recently, RNA editing by ADAR RNA adenosine deaminase enzymes has also been unveiled to influence ~~on~~ R-loop homeostasis (76). Nuclear-localized ADAR1p110 was shown to mediate R-loop-dependent genome instability at telomeres in cancer cells carrying non-canonical variants of telomeric repeats (Figure 2f). Notably, editing of A-C mismatches to I:C matched pairs by ADAR1p110 at DNA-RNA hybrids was observed to promote R-loop resolution by RNase H2. On the other hand, recent observations indicate that ADAR2 edits DNA-RNA hybrids to facilitate its dissolution close to DSBs and promote efficient DNA end resection and repair (77).

Conclusions and future perspectives

TRCs are an important endogenous source of DNA damage and genome instability, a hallmark of cancer cells. Interestingly, the epigenome is emerging as a key regulator of such TRCs and increasing evidence indicates that the functional chromatin network needs to be properly preserved to ensure genome integrity. Epigenetic mechanisms including DNA methylation, histone turnover and PTMs, histone chaperones, chromatin modifying and remodeling enzymes and RNA modification and edition limit TRCs helping preserve genome stability. Notably, chromatin factors involved in these processes are frequently altered in cancer, pointing to a direct connection between their deficiencies and the transformation process. Defining the molecular basis of this connection is essential to understand the causes and consequences of genome instability, frequently associated with cancer and some genetic diseases. Therefore, determining the underlying molecular mechanisms used by the cell to limit TRCs as a source of genome instability should help understand the transformation process and explore new therapeutic approaches of the disease. Future investigations should better define the impact of the chromatin network on the mechanisms that help prevent and resolve TRCs, as well as to test novel strategies such as those based on synthetic lethality, to specifically target malignant cells with high levels of TRC-driven genome instability. Thus, drugs targeting specific factors involved in this process may be used to selectively kill cancer cells and improve patient's prognosis.

AUTHOR CONTRIBUTIONS

A.B.-F and A.A. wrote the manuscript, discussed and agreed with the final version of this manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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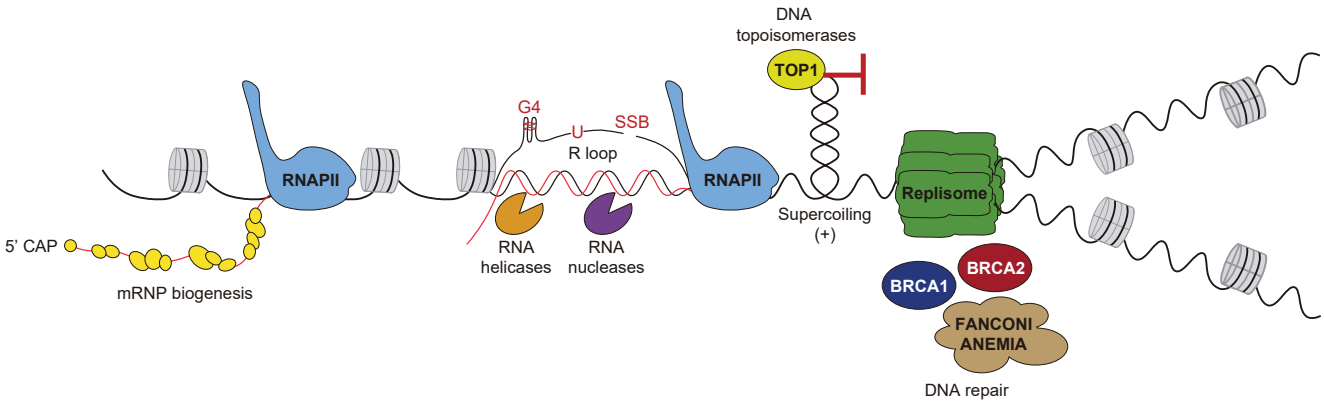
FIGURE LEGENDS

Figure 1. Transcription-associated obstacles to DNA replication.
Transcription occurs at the same template as DNA replication, posing an obstacle to RF progression that needs to be surpassed to proceed with efficient DNA duplication. The transcription machinery itself is tightly bound to DNA and this may impede RF progression. In addition, transcription induces the occurrence of additional structures such as DNA supercoiling, non-B DNA structures (R-loops; G4s), DNA damage or closed chromatin states that can further hinder DNA replication. Coordinated action of several cellular activities (messenger ribonucleoprotein (mRNP) biogenesis factors, RNA helicases, nucleases or topoisomerases) prevents the accumulation of such structures, and the DNA Damage Response (DDR) helps solve transcription-replication conflicts (TRCs).

Figure 2. Epigenetic mechanisms at transcription-replication collisions.
Multiple chromatin factors contribute to the prevention of TRCs to warrant genome integrity. **a**, Promoter proximal R-loops prevent DNMTs and promote DNA demethylation of CpG islands (CGI) and gene activation. **b**, Linker histones prevent unscheduled R-loops, which induce repressive epigenetic marks that may block RF progression. Aurora-A phosphorylate histone H3 serine 10 in S phase in response to R-loop formation. G9a and PRC are well-known interphase methyltransferase complexes that could be involved in histone H3 di/tri-methylation of lysine 9 in response to unscheduled R-loop accumulation. **c**, FACT and CAF-1 histone chaperons promote RF progression at transcribing loci. Evidence also indicates that ASF-1 could have a role in this process. **d**, Histone deacetylation complexes (Sin3A, Sirtuins) protect against R-loop-mediated genome instability. BRD4, which binds histone acetylated residues through its bromodomain, prevent R-loop-dependent genome instablity. Polycomb-repressive complexes 1 and 2 (PRC1, PRC2) and the G9a complex are also connected to R-loop metabolism. **e**, ATP-dependent chromatin remodelers have a major impact on TRCs. The SWI/SNF complex would act together with FANCD2 preventing TRCs, while INO80 complex prevent unscheduled R-loop formation and promote RNAPII release in response to TRCs. **f**, RNA modifications also influences R-loop occurrence. METTL3 methylates N6 position of adenosine ribonucleotides that have been suggested to drive cell cycle regulation of R-loop homeostasis through YTHDF2. TonEBP binds R-loops and recruits METTL3. Methylation of N5 position of cytosine ribonucleotide by TRDMT1 was shown to increase RAD52 affinity for DNA-RNA hybrids.

Figure 1


DNA
topoisomerases
TOP1
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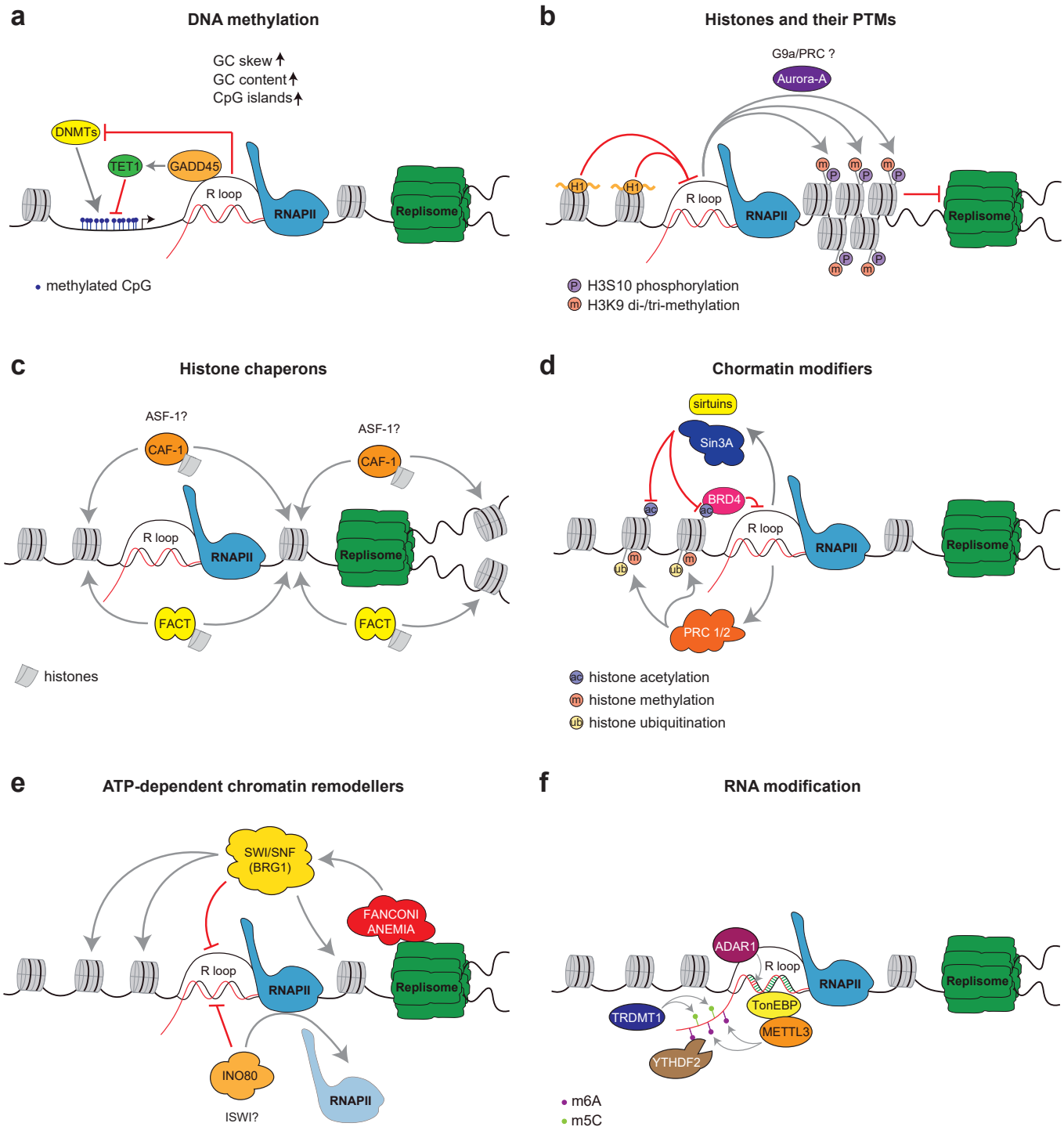
FANCONI
ANEMIA
DNA repair

Figure 2


a
DNA methylation
GC skew
GC content
CpG islands
DNMTs
TET1
GADD45
R loop
RNAPII
Replisome
methylated CpG
b
Histones and their PTMs
G9a/PRC ?
Aurora-A
H1
R loop
RNAPII
Replisome
H3S10 phosphorylation
H3K9 di-/tri-methylation
c
Histone chaperons
ASF-1?
CAF-1
R loop
RNAPII
Replisome
FACT
histones
d
Chormatin modifiers
sirtuins
Sin3A
BRD4
R loop
RNAPII
Replisome
PRC 1/2
histone acetylation
histone methylation
histone ubiquitination
e
ATP-dependent chromatin remodellers
SWI/SNF (BRG1)
FANCONI ANEMIA
R loop
RNAPII
Replisome
INO80
ISWI?
f
RNA modification
ADAR1
R loop
RNAPII
Replisome
TRDMT1
TonEBP
METTL3
YTHDF2
m6A
m5C