



Recent advances in understanding DNA replication: cell type-specific adaptation of the DNA replication program

Antoine Aze, Domenico Maiorano

► To cite this version:

Antoine Aze, Domenico Maiorano. Recent advances in understanding DNA replication: cell type-specific adaptation of the DNA replication program. F1000Research, 2018, 7, 10.12688/f1000research.15408.1 . hal-01887450

HAL Id: hal-01887450

<https://hal.science/hal-01887450>

Submitted on 8 Jun 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



Check for updates

REVIEW

Recent advances in understanding DNA replication: cell type-specific adaptation of the DNA replication program [version 1; peer review: 2 approved]

Antoine Aze, Domenico Maiorano 

Institute of Human Genetics, UMR9002, CNRS-University of Montpellier, Montpellier, 34396 Cedex 5, France

v1 First published: 29 Aug 2018, 7(F1000 Faculty Rev):1351 (<https://doi.org/10.12688/f1000research.15408.1>)Latest published: 29 Aug 2018, 7(F1000 Faculty Rev):1351 (<https://doi.org/10.12688/f1000research.15408.1>)**Abstract**

DNA replication is an essential process occurring prior to cell division. Cell division coupled to proliferation ensures the growth and renewal of a large variety of specialized cell types generated during embryonic development. Changes in the DNA replication program occur during development. Embryonic undifferentiated cells show a high replication rate and fast proliferation, whereas more differentiated cells are characterized by reduced DNA synthesis and a low proliferation rate. Hence, the DNA replication program must adapt to the specific features of cells committed to different fates. Recent findings on DNA synthesis regulation in different cell types open new perspectives for developing efficient and more adapted therapies to treat various diseases such as genetic diseases and cancer. This review will put the emphasis on recent progress made in this field.

Keywords

DNA synthesis, nucleus, chromatin, epigenetics, development, cell cycle, differentiation

Open Peer Review**Reviewer Status**  

	Invited Reviewers	
	1	2
version 1 published 29 Aug 2018		

F1000 Faculty Reviews are written by members of the prestigious **F1000 Faculty**. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

- 1 **Christian Speck**, Institute of Clinical Science, Imperial College, London, UK
- 2 **David MacAlpine**, Duke University Medical Center, Durham, USA
Rachel Hoffman, Duke University Medical Center, Durham, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Domenico Maiorano (domenico.maiorano@igh.cnrs.fr)

Author roles: **Aze A:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Maiorano D:** Supervision, Validation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: Research in DM's laboratory is supported by grants from "Fondation ARC pour la Recherche sur le Cancer", La Ligue contre le Cancer, INSERM, and MSD Avenir.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2018 Aze A and Maiorano D. This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Aze A and Maiorano D. **Recent advances in understanding DNA replication: cell type-specific adaptation of the DNA replication program [version 1; peer review: 2 approved]** F1000Research 2018, 7(F1000 Faculty Rev):1351 (<https://doi.org/10.12688/f1000research.15408.1>)

First published: 29 Aug 2018, 7(F1000 Faculty Rev):1351 (<https://doi.org/10.12688/f1000research.15408.1>)

Introduction

DNA synthesis occurs during the S phase of the cell cycle and is ensured by the replisome, a molecular machine made of a large number of proteins acting in a coordinated manner to synthesize DNA at many genomic locations, the replication origins¹. Replication origin activation in space and time (or replication program) is set by a sequence of events, starting already at the end of mitosis, lasting through G₁ phase, and ending in S phase when DNA replication is activated. These coordinated events ensure that the full genome will be replicated before mitosis since a faithful DNA synthesis is a prerequisite for genome integrity maintenance². DNA replication initiates from thousands of replication origins scattered along the chromosomes. Origins acquire the competence to replicate in a step called “licensing” that involves formation of a pre-replication complex (pre-RC), including loading of the replicative helicase MCM2-7 (recently reviewed³). Then once the transition from pre-RC to a pre-initiation complex (pre-IC) is induced by S-phase kinases, DNA replication is activated and DNA is unwound to provide the template for the replicative DNA polymerases^{2,4}.

The last 30 years of deep investigations in the DNA replication field have allowed the general mechanisms involved in eukaryotic DNA synthesis to be defined. Thanks to recent methodological improvements, such as genome-wide analysis^{5,6}, *in vitro* reconstitution assays^{7–9}, proteomics^{10–12}, and structural biology^{13,14}, our vision of the molecular pathways that govern DNA synthesis is becoming sharper.

Although the factors that drive DNA replication initiation are well conserved throughout the eukaryotic kingdom, cell type-specific differences in the regulation of this process within eukaryotes have been recently unraveled. From these studies, it appears that the regulation of DNA replication is influenced by the fate of a given cell. These findings shed new light on how the DNA replication program and the proliferation rate are being modulated during cell fate commitment, when cell type specialization is determined. New discoveries in this topic are undoubtedly essential to expand our understanding about the genesis of diseases and their progression. In this review, we will briefly describe recent achievements aiming to understand how the replication factors involved in the licensing, activation, and elongation steps of DNA synthesis adapt dynamically with cell fate determination to maintain genome integrity and homeostasis.

Coordination between replication origin licensing and G₁ length is critical for cell destiny

In vitro reconstitution assays in yeast have provided tremendous detailed information on how origins are licensed by dissecting the sequential biochemical steps involved^{3,7–9,14,15}. Detailed reviews covering the main features that characterize metazoan origins have been recently published^{3,5,16}. Briefly, in eukaryotes, replication origins are licensed through a chronological order that requires the binding of Origin Recognition Complex (ORC), Cdc6, and Cdt1 proteins onto chromatin^{17,18}. Two hexamers of the MCM2-7 helicase complex then are loaded in an inactive state prior to S phase (Figure 1). In yeast and mouse cells, Cdt1 and MCM2-7 form a complex before being recruited

onto replication origins by ORC and Cdc6^{19–21}. The MCM2-7 double hexamer must be activated by S-phase kinases to be able to unwind DNA and initiate DNA replication. However, MCM2-7 complexes are recruited in excess so that not all MCM2-7 complexes are activated during a cell cycle (Figure 1). The choice of the origins to be activated (around 30,000 in mammalian cells) is variable from cell to cell and ensures flexibility in origin usage during the DNA replication program to adapt with cell fate commitment, cell environment, and replicative stress^{22,23}. Origin mapping strategies coupled with high-throughput sequencing revealed that the chromatin context influences origin selection through genetic and epigenetic features located in close proximity to the origins.

It is now clear that most replication origins being constitutively activated across multiple metazoan cell types (hereafter named “shared origins”) are associated with unmethylated CpG islands, G-rich elements, transcriptional start sites, and histone modifications related to open chromatin marks (H3K4^{me3}, H3K9^{Ac}, and H3K27^{Ac})^{24–29}. Notably, this population of shared origins tends to initiate early during S phase, whereas cell type-specific origins initiate during late S-phase and are linked with compacted chromatin marks²⁸. These observations underline the relationship between chromatin modifications with the cellular context in origin selection.

Two independent studies describing reconstitution of DNA replication initiation events *in vitro* from chromatinized templates in yeast provided biochemical evidence that the regulatory functions of chromatin structure influence origin selection. These studies confirmed that nucleosome-free regions contribute to defining ORC binding and thus origin function^{30,31}, as previously suggested from genome-wide studies mapping ORC binding sites and nucleosome occupancy in various organisms^{32–36}. Moreover, in mouse embryonic stem (ES) cells, depletion of the histone H1 perturbs the landscape of replication origin activation³⁷. Because chromatin environment changes during cell fate commitment and in different cell types, it is generally assumed that the DNA replication program is coordinated with transcription to avoid transcription–replication conflicts and thus preserve genomic integrity. This seems particularly crucial during the onset of developmental programs and cell lineage specification. In *Caenorhabditis elegans*, origins from rapidly replicating pluripotent embryos coincide with open chromatin regions of highly transcribed genes, whereas establishment of the new transcriptional program, occurring at later embryonic stages when cell differentiation begins, correlates with the reorganization of replication initiation sites^{29,38}.

Permissive chromatin features for rapid activation of replication origins could influence the cell cycle length. ES cells have a shorter G₁ compared with their differentiated counterparts, which impacts on the licensing step. ES cells recruit much more MCM2-7 to the chromatin than tissue-specific stem cells or progenitor cells³⁹. This excess of origins that remain dormant during S phase appears to be important to maintain pluripotency^{40,41} and could also protect the genome against DNA replication stress occurring in ES cells^{39,42}.

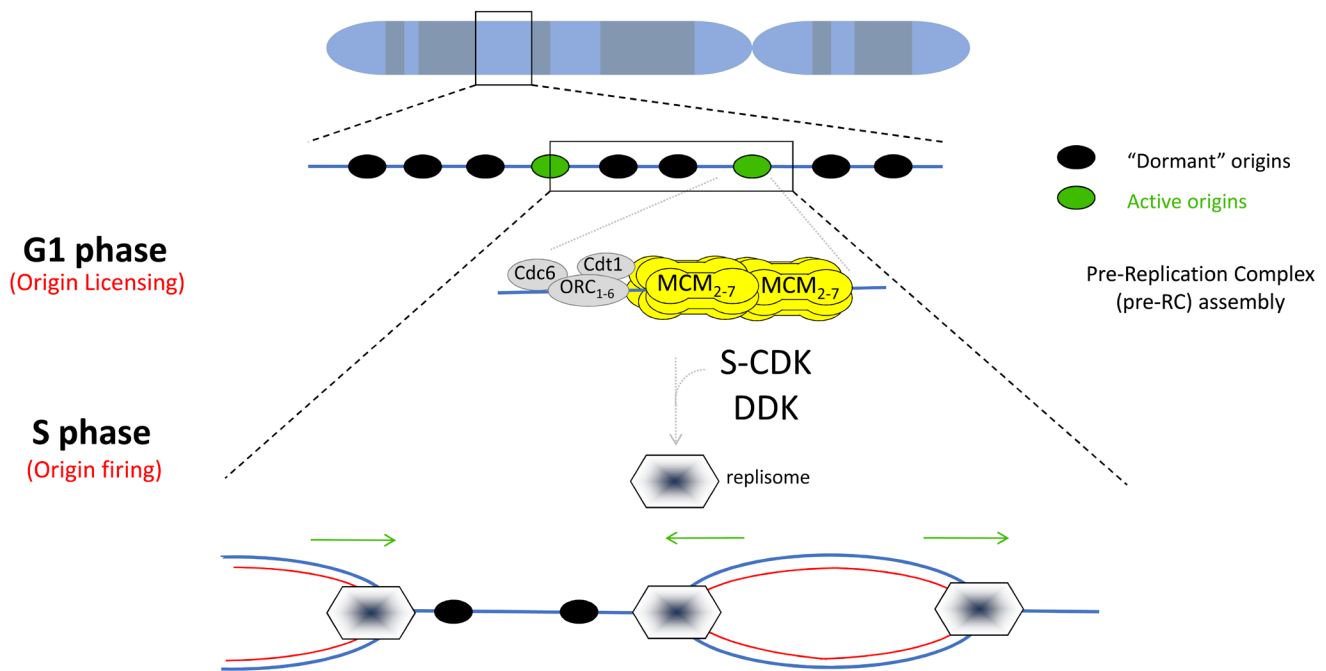


Figure 1. Replication of eukaryotic chromosomes. Replication origins are scattered along the genome to ensure that each chromosome is entirely replicated in S phase. Pre-replication complex (Pre-RC) assembly and origin activation are tightly regulated in a sequential manner to ensure that replication occurs only once per cell cycle. Hence, throughout the G₁ phase, origins are licensed by the sequential loading of the pre-RC components: Origin Recognition Complex (ORC), CDC6, CDT1, and (at the final stage) MCM2-7. Once a double MCM2-7 hexamer is stably recruited onto chromatin, origins are licensed. Many replication origins are licensed but few are activated, allowing a backup of origins to be used when DNA replication is perturbed. Origin firing occurs under the combined activities of S-phase Cyclin-Dependent Kinase (CDK) and Dbf4-Dependent Kinase (DDK), allowing the recruitment of additional factors involved in DNA replication initiation and elongation. MCM2-7, together with CDC45 and GINS, composes the DNA helicase that unwinds DNA in a bidirectional manner. The entire replication machinery made of accessory factors required for replication fork stability and the synthesis of DNA is called the replisome.

Besides changes in the kinetics by which MCM2-7 is loaded onto chromatin, licensing control adapts to G₁ length, suggesting that pre-RC binding is developmentally regulated. Indeed, quantitative single-cell analysis performed in human cells by Matson and colleagues demonstrated that origins are licensed faster in pluripotent cells compared with their isogenic differentiated counterparts and that loading of the MCM2-7 helicase slows down as G₁ duration is extended⁴³. The authors revealed that high expression of the licensing factor Cdt1 was important for fast MCM2-7 loading rates, thus enabling ES cells to rapidly license origins prior to the G₁-to-S phase transition. Similar to the need for additional dormant origins, fast licensing kinetics seems essential to ensure pluripotency in ES cells and induced pluripotent stem cells. This observation was corroborated by Carroll and colleagues in intestinal stem cells from adult tissues⁴⁴. The authors demonstrated that licensing is interconnected with the proliferative commitment of stem cells. They found that Lgr5⁺ intestinal stem cells, which contribute primarily to the renewal of the intestinal epithelium, reside mostly in a G₁, unlicensed state, although they express MCM2 and other proliferative markers to a level equivalent to the licensed population. Interestingly, this unlicensed state correlates with an elongated cell cycle that could be considered as a backup mechanism to sustain proliferative fate decisions and tissue maintenance. Nonetheless, the link between chromatin structures and adaptation to G₁ length in such a context remains to be determined.

Uncoupling of G₁ length with licensing kinetics has been observed during oncogenic transformation. Overexpression of oncogenes, such as cyclin E and c-MYC, shortens G₁ and forces cells to engage S phase earlier with incomplete licensing. Consequently, the replication program is perturbed, leading to accumulation of replication stress^{45,46}. Origin usage following oncogene activation was recently investigated genome-wide. The authors found that in these conditions new initiation zones, which were normally suppressed by transcription in G₁, appear in intragenic regions⁴⁷. These results also confirm an observation in *drosophila* showing that active transcription modulates MCM2-7 distribution⁴⁸. Nonetheless, how RNA polymerases inactivate and redistribute MCM2-7 remains to be determined. It has been reported that DNA translocases and RNA polymerases in yeast are able to push MCM2-7 along DNA, but similar processes have not yet been described in metazoans^{8,49}. An emerging picture from these studies is that cell cycle length, local chromatin structure, and active transcription can modulate the extent of origin licensing.

Activation of DNA replication in different cellular contexts: control in space and time matters

During S phase, origins are activated by the combined activities of cyclin-dependent kinase (CDK) and Dbf4-dependent kinase (DDK) kinases (Figure 1) targeting several substrates allowing the recruitment of CDC45 and GINS complex to

MCM2-7, thereby forming the CMG complex, the functional replicative helicase⁵⁰. Chromatin environment contributes to licensing as described previously through MCM2-7 loading but also to origin selection through MCM2-7 activation^{51,52}. The dynamics of origin activation during S phase follow a spatio-temporal order known as replication timing (Figure 2). Replication timing in eukaryotes controls activation of replication of large chromosomal domains and is mediated by genetic determinants, local histone modifications, and global chromatin organization⁵³. Thus, DNA sequence features that mediate licensing in vertebrates can also affect the time when origins will be activated. Origin G-rich repeated elements (OGREs) are prone to form G-quadruplexes (G4s). Their presence in the genome is associated with origin activity^{25,54}. Nucleosome organization at the proximity of origins was reported to modulate both origin licensing (as described above) and MCM2-7 helicase-dependent activation steps of initiation⁵⁵ in yeast and more recently in mammals³⁷. Different histone modifications and certain histone modifiers have been assigned in origin selection and the dynamics of their activation across S phase^{29,38,52,56–60}.

Several histone-modifying enzymes such as the methyltransferase PR-Set7 and the acetyltransferase HBO1 in complex with BRPF3 have been reported to have a role in activation of particular replication origins^{52,61}. More recently, a great deal of investigation has focused on the contribution of chromatin regulators in controlling the timing of activation through chromatin organization. The telomere-associated protein Rif1 interferes with DDK-dependent phosphorylation of MCM2-7 and modulates nuclear architecture by anchoring heterochromatin^{62,63}. Rif1 might organize replication-timing domains through its association with G4s to repress pre-RC activation until late S-phase^{63–65}. The ORC-associated protein ORCA/LRWD1 establishes a repressive chromatin environment at a subset of origins, thus priming them for late replication⁶⁶. The replication-initiation determinant protein RepID initiates replication in a sequence-specific manner by interacting with a subgroup of origins⁶⁷.

Modulation of origin activation in a cell type-specific manner depends upon global changes in chromosomal architecture and mainly occurs within large chromosome domains known

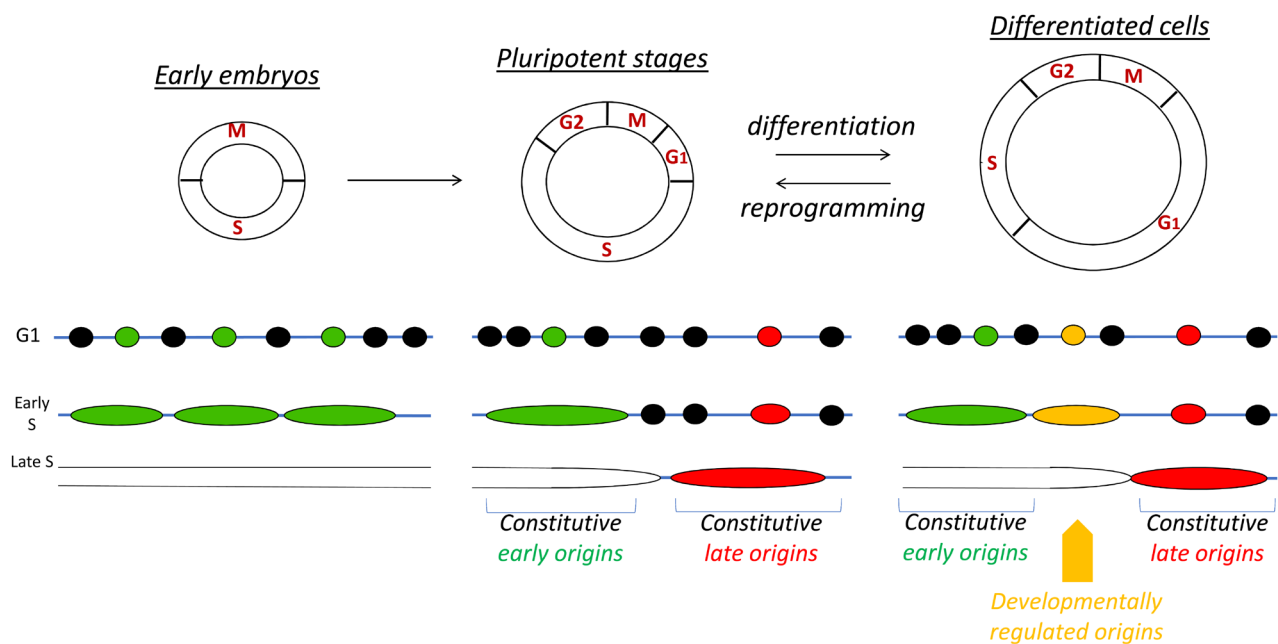


Figure 2. Replication program and cell features. Changes in the DNA replication program are dependent on cell features. In those rapidly dividing embryos, which are transcriptionally inactive, many replication origins fire to ensure fast S-phase. Selection of replication origins at this stage is believed to be random. Despite improvements in replication origin mapping, this idea has not yet been challenged. The timing of replication during early development is not clearly defined, as S-phase length is very short. During the pluripotency stage, appearance of gap phases and the onset of transcription confer a certain nuclear organization that sets the genome for a specific program of replication. Constitutive origins that replicate early are associated with strong origin density and efficiency, a high GC content, strong gene density, and nucleosome-free regions. On the other side, late constitutive origins are poor in origins and genes, GC content is low, and chromatin accessibility is restricted. Rif1 is a major factor shown to modulate origin activity for late replicating domains. The replication program changes dynamically during differentiation or cell lineage development, in coordination with changes in transcriptional activity and chromatin organization. Whereas constitutive origins are activated at the same location and with the same timing, some origins will be regulated following acquisitions of new cellular features. Remarkably, tumor development leads to formation of a heterogeneous population of cells, including cells with stem-like properties, progenitors, and differentiated tumor cells. These cells have the ability to perpetuate their lineage, to give rise to differentiated cells, and to undergo rapid growth. These molecular features, recapitulated during early embryonic development, illustrate similarities between cancer stem cells and embryogenesis. Understanding the DNA replication program regulation in a cell type-specific manner will allow investigation of the processes behind tumorigenesis from a different perspective.

as Topologically Associating Domains (TADs)^{68–71}. These constitute structurally distinct chromatin domains covering several megabases where DNA interactions are favored. TADs show a strong correlation with replication timing domains in which several replication units are concomitantly activated. Nuclear reorganization that accompanies differentiation and the establishment of developmental programs result in changes in replication timing of the human genome^{70,72,73}; notably, alterations in replication timing have been detected in several diseases^{74,75}.

Therefore, flexibility in origin activation seems critical to accommodate the dynamic changes in the transcriptional program and genome repositioning (Figure 2). Indeed, cell type-specific replication origins correlate with regions corresponding to differentiation-specific and tissue-specific gene expression programs^{76,77}. Origins that are activated in a cell type-dependent manner appear to replicate late in S phase²⁸. Histones and chromatin modifications described above impose a crosstalk between replication and transcription and are interconnected during differentiation and development^{29,38} although this relationship remains enigmatic.

Origin activation dynamics that determine replication timing therefore might play a role in establishing local and global chromatin structure to facilitate the cellular response to the differentiation process. Remarkably, establishment of TADs during early development in mammals requires DNA replication but not transcription⁷⁸. Moreover, perturbations in DNA replication during development can cause epigenetic changes (alleviation of repressive marks) potentially inherited by the next generations⁷⁹.

Chromatin organization immediately following fertilization in vertebrates is particularly critical for DNA replication initiation and this occurs in a transcription-independent manner following fertilization⁸⁰.

The capacity to selectively modulate origin usage in a cell type-specific manner suggests that the proteins involved in origin activation might play specific functions. Indeed, replication initiation proteins, and their availability during S phase, can be involved in dictating specificity in origin activation^{81–85}. The Sld3 vertebrate homolog Treslin/TICRR, a CDK target that acts as a binding site for TopBP1 and Mdm2 binding protein MTBP (both proteins being required for GINS-CDC45 recruitment), was proposed to link chromatin acetylation to DNA replication initiation efficiency and timing in different cancer cell lines^{58,86}. This observation shows that Rif1 is not the only known site-specific regulator of DNA replication initiation and timing. Likewise, a function in origin efficiency has been assigned to the Treslin partner MTBP, probably through its ability to localize Treslin near G4 structures⁸⁷. Finally, Rif1 accessibility to chromatin was recently implicated in determining the onset of late replication during embryonic development⁸⁸.

Overall, these studies suggest a functional interaction between components of the replication machinery with chromatin modifiers leading to reorganization of the genome architecture

during development. In turn, reorganization of the chromatin architecture defines cell type-specific transcriptional programs that feedback on the availability of replication proteins but equally on the replication timing by shaping chromatin architecture in specific domains such as TADs. Hence, genetic and epigenetic features set during developmental transitions may function as selective ways to repress or activate licensing or firing (or both) of a subset of origins, potentially within replication timing domains. Precise origin mapping at the single-molecule level in a single cell (using nanopore sequencing, for instance) completed by *in vitro* reconstitution assays using human proteins will undoubtedly bring to light new exciting concepts in this field.

Adaptation of the replisome to fast proliferation

A large variety of cell types critical for tissue function are formed during early embryonic development, when cell commitment first takes place. The proliferative state decision is variable for each cell type and may influence cell cycle duration. Consequently, steps required for proliferation, such as genome duplication, must be tightly regulated with cell cycle progression to maintain homeostasis. For instance, embryonic cell division in metazoans exhibits dramatic lengthening of the cell cycle at the onset of gastrulation, a stage required for cell type specialization and embryo patterning^{89,90}. Lengthening of the total cell cycle time is achieved mostly by extension of the G₁ phase and moderately the S phase⁹¹.

A variation in replisome composition following DNA replication perturbations or between different cell types was unraveled thanks to recent advances in quantitative proteomics at the replication forks^{11,92,93}. Analysis of the replication machinery at the forks by isolation of proteins on nascent DNA (iPOND) allows comparison of protein abundance at replication forks in different contexts. It was shown that replisomes of pluripotent stem cells contain a particular protein network that accommodates a high proliferative capacity with short cell cycle phases and reduced endogenous DNA replication stress⁹⁴. Factors involved in DNA repair, such as mismatch repair, but equally pluripotency and epigenetic inheritance factors, such as the NuRD-HDAC complex, were found to be enriched at replication forks. Interestingly, independent studies confirmed the requirement of a NuRD complex for DNA replication during early embryonic development⁹⁵. ES cells seem to require additional factors at the replication forks to cope with DNA replication perturbations. Thus, Filia-Floped was identified by iPOND as a new protein complex involved in resolution of stalled forks during a normal S-phase in mouse ES cells compared with their differentiated counterparts⁹⁶. It is likely that strategies set in stem cells to ensure fast DNA replication may also be exploited in other biological contexts requiring fast proliferation, including very early embryogenesis and tumorigenesis. For example, the Rad18 E3 ubiquitin ligase, a master regulator of translesion DNA synthesis, is an abundant component of the DNA replication machinery during *Xenopus* early development and confers to the replisome the ability to hijack DNA lesions and suppress the DNA damage response, ensuring fast cell cycle progression. Remarkably, Rad18 was found to be highly expressed in glioblastoma cancer stem cells⁹⁷.

Overall, these recent observations converge toward the idea that replisome composition can be selected “*a la carte*” regarding the biological features set by specific cell types. Consistent with this idea, replication of specific genome locations like telomeres, common fragile sites, or centromeres has been shown to involve particular DNA replication partners at the vicinity of the DNA replication fork to ensure stability of those genomic regions^{98–100}.

Conclusions

A defective DNA replication program is the source of several pathologies during development (Meier-Gorlin syndrome) and during the adult life (carcinogenesis)^{45,101}. Metazoan origins lack consensus sequences and are associated with different structural features that confer cell type-specific replication. Additional mechanisms operate to fine-tune pre-RC assembly, origin activity, and replisome composition. This allows cells to coordinate a fast replication program with their fate, contributing to genome integrity maintenance despite DNA replication perturbations often observed during tumorigenesis and development. Identification of various factors involved in origin selection and their activity in a cell type-specific manner is a great source of interest. Such factors may often be deregulated during cancer development; thus, their targeting might constitute effective anti-cancer therapies.

Nevertheless, these discoveries are only the tip of the iceberg as limited information is currently available regarding their regulation. Biochemistry, electron cryomicroscopy analysis, *in vitro* reconstitution assays using vertebrate proteins, and genomic approaches on single cells should largely contribute to breakthrough findings in the field.

Abbreviations

CDK, cyclin-dependent kinase; DDK, Dbf4-dependent kinase; ES, embryonic stem; G4, G-quadruplex; iPOND, isolation of proteins on nascent DNA; ORC, origin recognition complex; pre-RC, pre-replication complex; TAD, topological associated domain

Grant information

Research in DM's laboratory is supported by grants from “Fondation ARC pour la Recherche sur le Cancer”, La Ligue contre le Cancer, INSERM, and MSD Avenir.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We thank Philippe Pasero and Eric Morency for critical reading of the manuscript.

References



- Alabert C, Groth A: **Chromatin replication and epigenome maintenance**. *Nat Rev Mol Cell Biol.* 2012; **13**(3): 153–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Fragkos M, Ganier O, Coulombe P, *et al.*: **DNA replication origin activation in space and time**. *Nat Rev Mol Cell Biol.* 2015; **16**(6): 360–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hyrien O: **How MCM loading and spreading specify eukaryotic DNA replication initiation sites [version 1; referees: 4 approved]**. *F1000Res.* 2016; **5**: pii: F1000 Faculty Rev-2063.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Parker MW, Botchan MR, Berger JM: **Mechanisms and regulation of DNA replication initiation in eukaryotes**. *Crit Rev Biochem Mol Biol.* 2017; **52**(2): 107–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Prioleau MN, MacAlpine DM: **DNA replication origins-where do we begin?** *Genes Dev.* 2016; **30**(15): 1683–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Urban JM, Foulk MS, Casella C, *et al.*: **The hunt for origins of DNA replication in multicellular eukaryotes**. *F1000Prime Rep.* 2015; **7**: 30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Aguilar RR, Tyler JK: **Thinking Outside the Cell: Replicating Replication *In Vitro***. *Mol Cell.* 2017; **65**(1): 5–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Warner MD, Azmi IF, Kang S, *et al.*: **Replication origin-flanking roadblocks reveal origin-licensing dynamics and altered sequence dependence**. *J Biol Chem.* 2017; **292**(52): 21417–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Yeeles JTP, Janska A, Early A, *et al.*: **How the Eukaryotic Replisome Achieves Rapid and Efficient DNA Replication**. *Mol Cell.* 2017; **65**(1): 105–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Dungrawala H, Cortez D: **Purification of proteins on newly synthesized DNA using iPOND**. *Methods Mol Biol.* 2015; **1228**: 123–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Alabert C, Bukowski-Wills JC, Lee SB, *et al.*: **Nascent chromatin capture proteomics determines chromatin dynamics during DNA replication and identifies unknown fork components**. *Nat Cell Biol.* 2014; **16**(3): 281–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Cortez D: **Proteomic Analyses of the Eukaryotic Replication Machinery**. *Meth Enzymol.* 2017; **591**: 33–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Miller TC, Costa A: **The architecture and function of the chromatin replication machinery**. *Curr Opin Struct Biol.* 2017; **47**: 9–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Riera A, Barbon M, Noguchi Y, *et al.*: **From structure to mechanism—understanding initiation of DNA replication**. *Genes Dev.* 2017; **31**(11): 1073–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Diffley JF: **On the road to replication**. *EMBO Mol Med.* 2016; **8**(2): 77–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Marks AB, Fu H, Aladjem MI: **Regulation of Replication Origins**. *Adv Exp Med Biol.* 2017; **1042**: 43–59.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Maiorano D, Moreau J, Méchali M: **XCDT1 is required for the assembly of pre-replicative complexes in *Xenopus laevis***. *Nature.* 2000; **404**(6778): 622–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Maiorano D, Rul W, Méchali M: **Cell cycle regulation of the licensing activity of Cdt1 in *Xenopus laevis***. *Exp Cell Res.* 2004; **295**(1): 138–49.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Remus D, Beuron F, Tolun G, *et al.*: **Concerted loading of Mcm2-7 double hexamers around DNA during DNA replication origin licensing**. *Cell.* 2009; **139**(4): 719–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Tanaka S, Diffley JF: **Interdependent nuclear accumulation of budding yeast Cdt1 and Mcm2-7 during G1 phase**. *Nat Cell Biol.* 2002; **4**(3): 198–207.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- You Z, Masai H: **Cdt1 forms a complex with the minichromosome maintenance protein (MCM) and activates its helicase activity**. *J Biol Chem.* 2008; **283**(36): 24469–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

22. Méchali M: **Eukaryotic DNA replication origins: Many choices for appropriate answers.** *Nat Rev Mol Cell Biol.* 2010; 11(10): 728–38.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Yekezare M, Gómez-González B, Diffley JF: **Controlling DNA replication origins in response to DNA damage - inhibit globally, activate locally.** *J Cell Sci.* 2013; 126(Pt 6): 1297–306.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. **F** Besnard E, Babled A, Lapasset L, *et al.*: **Unraveling cell type-specific and reprogrammable human replication origin signatures associated with G-quadruplex consensus motifs.** *Nat Struct Mol Biol.* 2012; 19(8): 837–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
25. Cayrou C, Ballester B, Peiffer I, *et al.*: **The chromatin environment shapes DNA replication origin organization and defines origin classes.** *Genome Res.* 2015; 25(12): 1873–85.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. **F** Langley AR, Gräf S, Smith JC, *et al.*: **Genome-wide identification and characterisation of human DNA replication origins by initiation site sequencing (ini-seq).** *Nucleic Acids Res.* 2016; 44(21): 10230–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
27. Picard F, Cadoret JC, Audit B, *et al.*: **The spatiotemporal program of DNA replication is associated with specific combinations of chromatin marks in human cells.** *PLoS Genet.* 2014; 10(5): e1004282.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. **F** Smith OK, Kim R, Fu H, *et al.*: **Distinct epigenetic features of differentiation-regulated replication origins.** *Epigenetics Chromatin.* 2016; 9: 18.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
29. **F** Rodríguez-Martínez M, Pinzón N, Ghomidh C, *et al.*: **The gastrula transition reorganizes replication-origin selection in *Caenorhabditis elegans*.** *Nat Struct Mol Biol.* 2017; 24(3): 290–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
30. **F** Devbhandari S, Jiang J, Kumar C, *et al.*: **Chromatin Constrains the Initiation and Elongation of DNA Replication.** *Mol Cell.* 2017; 65(1): 131–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
31. **F** Kurat CF, Yeeles JTP, Patel H, *et al.*: **Chromatin Controls DNA Replication Origin Selection, Lagging-Strand Synthesis, and Replication Fork Rates.** *Mol Cell.* 2017; 65(1): 117–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
32. **F** Berbenetz NM, Nislow C, Brown GW: **Diversity of eukaryotic DNA replication origins revealed by genome-wide analysis of chromatin structure.** *PLoS Genet.* 2010; 6(9): e1001092.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
33. **F** Eaton ML, Galani K, Kang S, *et al.*: **Conserved nucleosome positioning defines replication origins.** *Genes Dev.* 2010; 24(8): 748–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
34. **F** Lubelsky Y, Sasaki T, Kuipers MA, *et al.*: **Pre-replication complex proteins assemble at regions of low nucleosome occupancy within the Chinese hamster dihydrofolate reductase initiation zone.** *Nucleic Acids Res.* 2011; 39(8): 3141–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
35. **F** Miotto B, Ji Z, Struhl K: **Selectivity of ORC binding sites and the relation to replication timing, fragile sites, and deletions in cancers.** *Proc Natl Acad Sci U S A.* 2016; 113(33): E4810–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
36. Rodríguez J, Lee L, Lynch B, *et al.*: **Nucleosome occupancy as a novel chromatin parameter for replication origin functions.** *Genome Res.* 2017; 27(2): 269–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. **F** Almeida R, Fernández-Justel JM, Santa-María C, *et al.*: **Chromatin conformation regulates the coordination between DNA replication and transcription.** *Nat Commun.* 2018; 9(1): 1590.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
38. **F** Pourkarimi E, Bellush JM, Whitehouse I: **Spatiotemporal coupling and decoupling of gene transcription with DNA replication origins during embryogenesis in *C. elegans*.** *eLife.* 2016; 5: pii: e21728.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
39. Ge XQ, Han J, Cheng EC, *et al.*: **Embryonic Stem Cells License a High Level of Dormant Origins to Protect the Genome against Replication Stress.** *Stem Cell Reports.* 2015; 5(2): 185–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
40. Karet MS, Sage J, Wernig M: **Crosstalk between stem cell and cell cycle machineries.** *Curr Opin Cell Biol.* 2015; 37: 68–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. **F** Soufi A, Dalton S: **Cycling through developmental decisions: How cell cycle dynamics control pluripotency, differentiation and reprogramming.** *Development.* 2016; 143(23): 4301–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
42. Ahuja AK, Jodkowska K, Teloni F, *et al.*: **A short G1 phase imposes constitutive replication stress and fork remodelling in mouse embryonic stem cells.** *Nat Commun.* 2016; 7: 10660.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. **F** Matson JP, Dumitru R, Coryell P, *et al.*: **Rapid DNA replication origin licensing protects stem cell pluripotency.** *eLife.* 2017; 6: pii: e30473.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
44. **F** Carroll TD, Newton IP, Chen Y, *et al.*: **Lgr5⁺ intestinal stem cells reside in an unlicensed G₁ phase.** *J Cell Biol.* 2018; 217(5): 1667–85.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
45. Macheret M, Halazonetis TD: **DNA replication stress as a hallmark of cancer.** *Annu Rev Pathol.* 2015; 10: 425–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Yang Y, Gao Y, Mutter-Rottmayer L, *et al.*: **DNA repair factor RAD18 and DNA polymerase Polk confer tolerance of oncogenic DNA replication stress.** *J Cell Biol.* 2017; 216(10): 3097–115.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. **F** Macheret M, Halazonetis TD: **Intragenic origins due to short G1 phases underlie oncogene-induced DNA replication stress.** *Nature.* 2018; 555(7694): 112–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
48. **F** Powell SK, MacAlpine HK, Prinz JA, *et al.*: **Dynamic loading and redistribution of the Mcm2-7 helicase complex through the cell cycle.** *EMBO J.* 2015; 34(4): 531–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. **F** Gros J, Kumar C, Lynch G, *et al.*: **Post-licensing Specification of Eukaryotic Replication Origins by Facilitated Mcm2-7 Sliding along DNA.** *Mol Cell.* 2015; 60(5): 797–807.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. Burgers PMJ, Kunkel TA: **Eukaryotic DNA Replication Fork.** *Annu Rev Biochem.* 2017; 86: 417–38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
51. **F** Das SP, Borman T, Liu VW, *et al.*: **Replication timing is regulated by the number of MCMs loaded at origins.** *Genome Res.* 2015; 25(12): 1886–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. **F** Feng Y, Vlassis A, Roques C, *et al.*: **BRPF3-HBO1 regulates replication origin activation and histone H3K14 acetylation.** *EMBO J.* 2016; 35(2): 176–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
53. **F** Rivera-Mulia JC, Gilbert DM: **Replicating Large Genomes: Divide and Conquer.** *Mol Cell.* 2016; 62(5): 756–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
54. Cayrou C, Coulombe P, Vigneron A, *et al.*: **Genome-scale analysis of metazoan replication origins reveals their organization in specific but flexible sites defined by conserved features.** *Genome Res.* 2011; 21(9): 1438–49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. **F** Azmi IF, Watanabe S, Maloney MF, *et al.*: **Nucleosomes influence multiple steps during replication initiation.** *eLife.* 2017; 6: pii: e22512.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. Liu J, McConnell K, Dixon M, *et al.*: **Analysis of model replication origins in *Drosophila* reveals new aspects of the chromatin landscape and its relationship to origin activity and the prereplicative complex.** *Mol Biol Cell.* 2012; 23(1): 200–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
57. Rondinelli B, Schwerer H, Antonini E, *et al.*: **H3K4me3 demethylation by the histone demethylase KDM5C/JARID1C promotes DNA replication origin firing.** *Nucleic Acids Res.* 2015; 43(5): 2560–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. **F** Sansam CG, Pietrzak K, Majchrzycka B, *et al.*: **A mechanism for epigenetic control of DNA replication.** *Genes Dev.* 2018; 32(3–4): 224–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
59. **F** Tardat M, Brustel J, Kirsh O, *et al.*: **The histone H4 Lys 20 methyltransferase PR-Set7 regulates replication origins in mammalian cells.** *Nat Cell Biol.* 2010; 12(11): 1086–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
60. **F** Wu R, Wang Z, Zhang H, *et al.*: **H3K9me3 demethylase Kdm4d facilitates the formation of pre-initiative complex and regulates DNA replication.** *Nucleic Acids Res.* 2017; 45(1): 169–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
61. **F** Brustel J, Kirstein N, Izard F, *et al.*: **Histone H4K20 tri-methylation at late-firing origins ensures timely heterochromatin replication.** *EMBO J.* 2017; 36(18): 2726–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
62. **F** Alver RC, Chadha GS, Gillespie PJ, *et al.*: **Reversal of DDK-Mediated MCM Phosphorylation by Rif1-PP1 Regulates Replication Initiation and Replisome Stability Independently of ATR/Chk1.** *Cell Rep.* 2017; 18(10): 2508–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
63. **F** Foti R, Gnan S, Cornacchia D, *et al.*: **Nuclear Architecture Organized by Rif1 Underpins the Replication-Timing Program.** *Mol Cell.* 2016; 61(2): 260–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

64. Kanoh Y, Matsumoto S, Fukatsu R, *et al.*: **Rif1 binds to G quadruplexes and suppresses replication over long distances.** *Nat Struct Mol Biol.* 2015; **22**(11): 889–97.
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Mattarocci S, Shyian M, Lemmens L, *et al.*: **Rif1 controls DNA replication timing in yeast through the PP1 phosphatase Glc7.** *Cell Rep.* 2014; **7**(1): 62–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. **F** Wang Y, Khan A, Marks AB, *et al.*: **Temporal association of ORCA/LRWD1 to late-firing origins during G1 dictates heterochromatin replication and organization.** *Nucleic Acids Res.* 2017; **45**(5): 2490–502.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
67. **F** Zhang Y, Huang L, Fu H, *et al.*: **A replicator-specific binding protein essential for site-specific initiation of DNA replication in mammalian cells.** *Nat Commun.* 2016; **7**: 11748.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
68. Gilbert DM, Takebayashi SI, Ryba T, *et al.*: **Space and time in the nucleus: Developmental control of replication timing and chromosome architecture.** *Cold Spring Harb Symp Quant Biol.* 2010; **75**: 143–53.
[PubMed Abstract](#) | [Publisher Full Text](#)
69. Pope BD, Hiratani I, Gilbert DM: **Domain-wide regulation of DNA replication timing during mammalian development.** *Chromosome Res.* 2010; **18**(1): 127–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. Rhind N, Gilbert DM: **DNA replication timing.** *Cold Spring Harb Perspect Biol.* 2013; **5**(8): a010132.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
71. **F** Dixon JR, Selvaraj S, Yue F, *et al.*: **Topological domains in mammalian genomes identified by analysis of chromatin interactions.** *Nature.* 2012; **485**(7398): 376–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
72. **F** Pope BD, Ryba T, Dileep V, *et al.*: **Topologically associating domains are stable units of replication-timing regulation.** *Nature.* 2014; **515**(7527): 402–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
73. **F** Rivera-Mulia JC, Gilbert DM: **Replication timing and transcriptional control: Beyond cause and effect-part III.** *Curr Opin Cell Biol.* 2016; **40**: 168–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
74. **F** Rivera-Mulia JC, Desprat R, Trevilla-Garcia C, *et al.*: **DNA replication timing alterations identify common markers between distinct progeroid diseases.** *Proc Natl Acad Sci U S A.* 2017; **114**(51): E10972–E10980.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
75. **F** Sasaki T, Rivera-Mulia JC, Vera D, *et al.*: **Stability of patient-specific features of altered DNA replication timing in xenografts of primary human acute lymphoblastic leukemia.** *Exp Hematol.* 2017; **51**: 71–82.e3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
76. **F** Gerhardt J, Tomishima MJ, Zaninovic N, *et al.*: **The DNA replication program is altered at the FMR1 locus in fragile X embryonic stem cells.** *Mol Cell.* 2014; **53**(1): 19–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
77. **F** Norio P, Kosiyatrakul S, Yang Q, *et al.*: **Progressive activation of DNA replication initiation in large domains of the immunoglobulin heavy chain locus during B cell development.** *Mol Cell.* 2005; **20**(4): 575–87.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
78. **F** Ke Y, Xu Y, Chen X, *et al.*: **3D Chromatin Structures of Mature Gametes and Structural Reprogramming during Mammalian Embryogenesis.** *Cell.* 2017; **170**(2): 367–381.e20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
79. **F** Klosin A, Reis K, Hidalgo-Carcedo C, *et al.*: **Impaired DNA replication derepresses chromatin and generates a transgenerationally inherited epigenetic memory.** *Sci Adv.* 2017; **3**(8): e1701143.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
80. Aze A, Fragkos M, Bocquet S, *et al.*: **RNAs coordinate nuclear envelope assembly and DNA replication through ELYS recruitment to chromatin.** *Nat Commun.* 2017; **8**(1): 2130.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
81. **F** Mantiero D, Mackenzie A, Donaldson A, *et al.*: **Limiting replication initiation factors execute the temporal programme of origin firing in budding yeast.** *EMBO J.* 2011; **30**(23): 4805–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
82. **F** Patel PK, Komajosyula N, Rosebrock A, *et al.*: **The Hsk1(Cdc7) replication kinase regulates origin efficiency.** *Mol Biol Cell.* 2008; **19**(12): 5550–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
83. **F** Tanaka S, Nakato R, Katou Y, *et al.*: **Origin association of Sld3, Sld7, and Cdc45 proteins is a key step for determination of origin-firing timing.** *Curr Biol.* 2011; **21**(24): 2055–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
84. **F** Wong PG, Winter SL, Zaika E, *et al.*: **Cdc45 limits replicon usage from a low density of preRCs in mammalian cells.** *PLoS One.* 2011; **6**(3): e17533.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
85. **F** Wu PY, Nurse P: **Establishing the program of origin firing during S phase in fission Yeast.** *Cell.* 2009; **136**(5): 852–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
86. Sansam CG, Goins D, Siefert JC, *et al.*: **Cyclin-dependent kinase regulates the length of S phase through TICRR/TRESLIN phosphorylation.** *Genes Dev.* 2015; **29**(5): 555–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. **F** Kumagai A, Dunphy WG: **MTBP, the partner of Treslin, contains a novel DNA-binding domain that is essential for proper initiation of DNA replication.** *Mol Biol Cell.* 2017; **28**(22): 2998–3012.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
88. **F** Seller CA, O'Farrell PH: **Rif1 prolongs the embryonic S phase at the *Drosophila* mid-blastula transition.** *PLoS Biol.* 2018; **16**(5): e2005687.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
89. Artus J, Cohen-Tannoudji M: **Cell cycle regulation during early mouse embryogenesis.** *Mol Cell Endocrinol.* 2008; **282**(1–2): 78–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
90. O'Farrell PH, Stumpff J, Su TT: **Embryonic cleavage cycles: how is a mouse like a fly?** *Curr Biol.* 2004; **14**(1): R35–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
91. MacAuley A, Werb Z, Mirkes PE: **Characterization of the unusually rapid cell cycles during rat gastrulation.** *Development.* 1993; **117**(3): 873–83.
[PubMed Abstract](#)
92. Cortez D: **Preventing replication fork collapse to maintain genome integrity.** *DNA Repair (Amst).* 2015; **32**: 149–57.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
93. Dugrawala H, Rose KL, Bhat KP, *et al.*: **The Replication Checkpoint Prevents Two Types of Fork Collapse without Regulating Replicative Stability.** *Mol Cell.* 2015; **59**(6): 998–1010.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
94. Aranda S, Rutishauser D, Ernors P: **Identification of a large protein network involved in epigenetic transmission in replicating DNA of embryonic stem cells.** *Nucleic Acids Res.* 2014; **42**(11): 6972–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
95. **F** Christov CP, Dingwell KS, Skehel M, *et al.*: **A NuRD Complex from *Xenopus laevis* Eggs Is Essential for DNA Replication during Early Embryogenesis.** *Cell Rep.* 2018; **22**(9): 2265–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
96. **F** Zhao B, Zhang W, Cun Y, *et al.*: **Mouse embryonic stem cells have increased capacity for replication fork restart driven by the specific Filia-Floped protein complex.** *Cell Res.* 2018; **28**(1): 69–89.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
97. Kermi C, Prieto S, van der Laan S, *et al.*: **RAD18 is a Maternal Limiting Factor Silencing the UV-Dependent DNA Damage Checkpoint in *Xenopus* Embryos.** *Dev Cell.* 2015; **34**(3): 364–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
98. **F** Aze A, Sannino V, Soffientini P, *et al.*: **Centromeric DNA replication reconstitution reveals DNA loops and ATR checkpoint suppression.** *Nat Cell Biol.* 2016; **18**(6): 684–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
99. **F** Drosopoulos WC, Kosiyatrakul ST, Schildkraut CL: **BLM helicase facilitates telomere replication during leading strand synthesis of telomeres.** *J Cell Biol.* 2015; **210**(2): 191–208.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
100. **F** Madireddy A, Kosiyatrakul ST, Boisvert RA, *et al.*: **FANCD2 Facilitates Replication through Common Fragile Sites.** *Mol Cell.* 2016; **64**(2): 388–404.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
101. Bicknell LS, Bongers EM, Leitch A, *et al.*: **Mutations in the pre-replication complex cause Meier-Gorlin syndrome.** *Nat Genet.* 2011; **43**(4): 356–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:



Editorial Note on the Review Process

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1 David MacAlpine

Department of Pharmacology and Cancer Biology, Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, USA, Durham, USA

Rachel Hoffman

Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, USA

Competing Interests: No competing interests were disclosed.

2 Christian Speck

DNA Replication Group, Institute of Clinical Science, Imperial College, London, UK

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research