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Chromosome Research (2010) 18:137–145
DOI 10.1007/s10577-009-9105-3

Programming DNA replication origins and chromosome organization

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Published online: 12 January 2010
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Abstract During each cell cycle, thousands of DNA replication origins are activated in each cell of a metazoan organism. Although they appear site-specific, their usage and organization are rather plastic. Moreover, no strict sequence specificity has been observed in contrast to bacterial or *Saccharomyces cerevisiae* DNA replication origins. Epigenetic regulation linked to chromatin structure, chromosome organization, and transcription has been suggested to explain how DNA replication origins are selected and recognized by replication initiation factors. In this paper, we review these epigenetic features and discuss how, during the previous mitosis, chromosomal architecture might prepare DNA replication origins for a new cell cycle.

Keywords DNA replication origin · Chromatin · Nucleosome · DNA Loops · Transcription · Mitosis · Reprogramming

Abbreviations

Abf1	Autonomously replicating sequence binding factor 1
ACF	ATP-dependent chromatin assembly and remodeling factor
ARS	Autonomously replicating sequence
AT-rich	DNA sequences rich in adenine and thymine
ATPases	Adenosine triphosphatase
BrdUTP	Bromodeoxyuridine triphosphate
c-myc	Cellular homolog of the oncogene from myelocytomatosis virus
CDC6	Cell division cycle 6, an ATPase required for pre-RC formation
Cdt1	Cdc10-dependent transcript, a factor required for pre-RC formation
CHRAC	Chromatin accessibility complex
CpG	Cytosine guanine dinucleotide
DHFR	Dihydrofolate reductase
EBV	Epstein–Barr virus
G–S period	Transition between G1 (gap 1) and S (DNA synthesis) phase of the cell cycle
Gcn5	General control of amino acid synthesis 5, a histone acetyltransferase
H3 and H4	Histone H3 and H4
HAT	Histone acetyltransferase
HBO1	Histone acetyltransferase binding to ORC 1
HDAC	Histone deacetylase
ING	Inhibitor of growth
Jade-1	Gene for apoptosis and differentiation in epithelia-1

Responsible Editor: Marie-Noëlle Prioleau and Dean Jackson.

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LiS	Lithium 3,5-diiodosalicylate
MARs	Matrix attachment regions
MCM	Mini-chromosome maintenance
ORC	Origin recognition complex
OriP	Origin of plasmid replication
poly-dA/dT	DNA sequences containing tracks of adenine and thymine
pre-RC	Pre-replication complex
rDNA	Ribosomal RNA genes
Rpd3	Reduced potassium dependency 3, a histone deacetylase
SARs	Scaffold attachment regions
Sir2	Silent information regulator 2, a histone deacetylase
SNF2H	Sucrose nonfermenting protein 2 homolog, ATPase component of chromatin remodeling complexes
ySWI/SNF	SWItch/sucrose nonfermentable, a yeast nucleosome remodeling complex

Introduction

In any living organism, the entire genome should be faithfully duplicated during each cell cycle. DNA replication starts at DNA replication origins that must be activated only once during each S phase in order to maintain genome integrity. In *Escherichia coli*, a single DNA replication origin is sufficient to replicate the whole bacterial genome. This initiation site is at a fixed position in the genome and is defined by a strict genetic sequence (Jacob et al. 1963). In the unicellular eukaryote *Saccharomyces cerevisiae,* multiple DNA replication origins are also specified by a consensus sequence called autonomously replicating sequence (ARS). On the other hand, in *Saccharomyces pombe*, DNA replication origins do not have such consensus sequences and appear to rely on AT-rich islands (Dai et al. 2005; Heichinger et al. 2006; Segurado et al. 2003) and poly-dA/dT tracks (Okuno et al. 1999) for initiation. In multicellular organisms, no clear consensus sequence that characterizes replication origins has been identified to date. Moreover, origin recognition complexes (ORCs) that bind to DNA replication origins do not have a specificity for a particular sequence in vitro, suggesting that DNA replication origin position is not specified by DNA sequence alone (Vashee et al. 2003). In human or mouse cells, 30,000–50,000 DNA replication origins are activated at each cell cycle. In recent genome-wide analyses, some of these initiation sites have been mapped and shown to lie close to gene promoters that contained CpG islands (Cadoret et al. 2008; Sequeira-Mendes et al. 2009; our unpublished results). The absence of strict consensus sequences to define metazoan DNA replication origins led to question whether epigenetic mechanisms linked to chromatin structure and transcription might be the main determinants of replication origin localization in higher eukaryotes (Mechali 2001) for a review). In this paper, we review how genome organization could influence DNA replication origin localization and the plasticity of this localization during cell differentiation and reprogramming.

Influence of chromatin structure on origin localization and activation

In the nucleus, DNA is not naked but packaged with highly conserved histone proteins to form the basal element of chromatin structure: the nucleosome (Khorasanizadeh 2004). Accessibility to DNA sequence information could be therefore hindered by chromatin. However, chromatin features also serve as recognition marks for replication factors. Histone association with DNA is subjected to considerable regulation that can change the accessibility to a specific DNA sequence. Two major mechanisms are essential for modulating nucleosome organization and regulating access to the underlying DNA during the formation of the pre-replication complex (pre-RC): nucleosome remodeling and modification of the histone tails.

Nucleosome remodeling

In order to allow recognition of DNA replication origins and formation of the replication complex, it is believed that DNA replication origins should be either nucleosome-free or contain nucleosomes that can be easily displaced. Indeed, DNA replication origins are usually enriched in open chromatin structures (Audit et al. 2009; Field et al. 2008; Zhou et al. 2005). Moreover, the formation of the replication complex requires several proteins in addition to ORC (reviewed in this issue), and thus, it is unlikely that it could accommodate the presence of fixed nucleosomes.

Pioneer experiments in *S. cerevisiae* showed that the positioning of a nucleosome at a DNA replication origin inhibits initiation of replication at that origin (Simpson 1990). Similarly, Sir2 histone deacetylase inhibits DNA replication origin activity by favoring an unsuitable positioning of nucleosomes at DNA replication origins in *S. cerevisiae* (Crampton et al. 2008). The ORC complex may facilitate the formation of the pre-RC by influencing the positioning of nucleosomes (Lipford and Bell 2001).

Two major categories of nucleosome modifications have been implicated in the different processes of DNA replication. The first one, remodeling, concerns the movement and re-localization of nucleosomes relative to DNA sequences. Remodeling is carried out by members of a large family of ATPases which constitute the catalytic subunit of multi-protein complexes (Morettini et al. 2008). These complexes are involved in nucleosomal sliding (changes in nucleosome position relative to the DNA sequence) and nucleosome displacement (removal of histone octamers from DNA; Rippe et al. 2007). The second one concerns complexes that direct post-transcriptional histone modifications (Kouzarides 2007). This mechanism controls chromatin access by adding or removing covalent modifications (such as acetylation, methylation, phosphorylation, ribosylation, or ubiquitylation) on the N-terminal tails of histones. Nucleosomal positioning at DNA replication origins is regulated by different remodeling complexes. Knockdown of the catalytic subunit *SNF2H*, a member of the human chromatin accessibility complex (CHRAC) and ATP-dependent chromatin assembly and remodeling factor (ACF) complexes, decreases MCM3 binding to the Epstein–Barr virus DNA replication origin OriP and reduces origin firing (Zhou et al. 2005). Also, ySWI/SNF increases replication efficiency by stabilizing minichromosomes and increasing DNA replication origin initiation in *S. cerevisiae* (Flanagan and Peterson 1999). ISWI and ACF1 have especially important roles for replication of late-replicating regions (Collins et al. 2002; Vincent et al. 2008).

Transcription and DNA replication origins

Chromatin remodeling at DNA replication origins might also be a consequence of transcriptional regulation of the genes associated with these origins. The presence of transcription factor-binding motifs is an important determinant of nucleosome depletion (Bernstein et al. 2004; Yuan et al. 2005). In *S. cerevisiae*, DNA replication origins contain binding sites for the transcription factor Abf1 that could help origin activation (Diffley and Stillman 1989). In *S. pombe* as well as in higher eukaryotes, DNA replication origins are often located at promoters (Cadoret et al. 2008; Dai et al. 2005; Sequeira-Mendes et al. 2009; our unpublished data). Transcription factors can affect DNA replication origin localization or activation in different systems (Cheng et al. 1992; Danis et al. 2004; Ghosh et al. 2004; Maric et al. 2003; Minami et al. 2006; Sasaki et al. 2006). This could be achieved by recruiting chromatin remodeling and histone-modifying complexes (Fig. 1) or by a direct interaction with pre-RC components (Kohzaki and Murakami 2005 for review).

Generally, transcriptionally active promoters are hyper-acetylated on histones H3 and H4 (Berger 2007) and as a result maintain an open chromatin structure, which is a favorable substrate for initiation of DNA replication. Gcn5, a histone acetyl transferase (HAT) that is associated with transcriptional activity (Rodriguez-Navarro 2009), increases DNA replication when it is tethered to a yeast DNA replication origin (Vogelauer et al. 2002).

Chromatin modifications at DNA replication origins

Temperature-sensitive mutations in the pre-replication complex components ORC, CDC6, and MCM can be suppressed by inactivation of SIR2, a histone deacetylase (HDAC; Pappas et al. 2004). The HDAC Sir2p is also a negative regulator of chromosomal DNA replication (Pappas et al. 2004) and controls the frequency of DNA replication origin firing within rDNA (Pasero et al. 2002). Some yeast ARS elements contain specific sequences recognized by Sir2p that inhibit DNA replication origin activity, most likely by affecting the local chromatin structure (Crampton et al. 2008). Consistent with these observations, targeting the Rpd3 HDAC to a *Drosophila* DNA replication origin decreased its activity. Conversely, Chameau, the HAT responsible for DNA replication origin activation, increased H4 acetylation at ORC binding sites, leading to stronger origin activity (Aggarwal and Calvi 2004). Interestingly, the mammalian homologue of Chameau

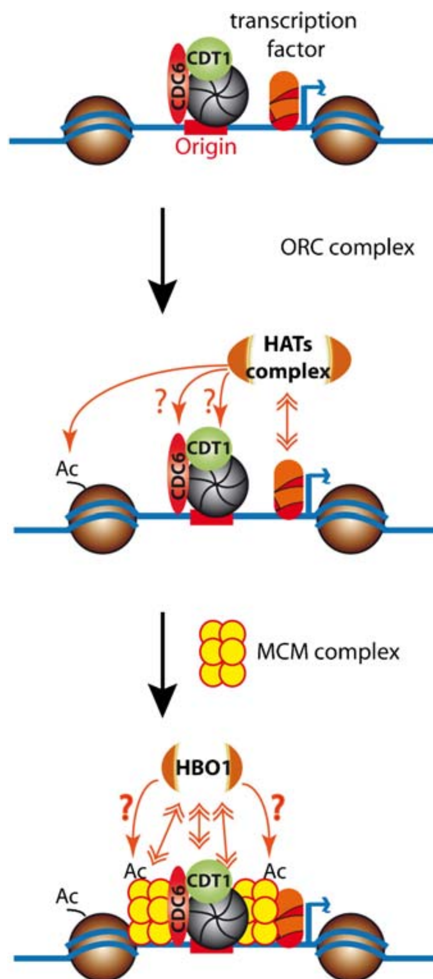

Fig. 1 Interplay between transcription factors, acetylation and DNA replication origin recognition. The ORC complex binds to an origin of DNA replication in the vicinity of a transcription factor. By recruiting HAT complexes, transcription factors can induce pre-RC activation through modification of ORC, CDT1, or CDC6. HAT complexes also acetylate surrounding nucleosomes and provide an environment favorable to recruitment of MCMs complexes onto chromatin. HBO1 might further acetylate one or more subunits of the MCM complex

is histone acetyltransferase binding to ORC 1 (HBO1), the catalytic subunit of a multi-protein complex that includes two tumor suppressor proteins, ING4 and 5, and two regulatory isoforms of the JADE-1 protein (Doyon et al. 2006); HBO1 derives its name from the ability to interact with ORC1 and MCM2 (Burke et al. 2001; Iizuka and Stillman 1999).

HBO1 is found in two different complexes (Fig. 2), one with ING4 (for transcription activity) and another one with ING5 (for DNA replication activity), which also contains three subunits of the MCM helicase that binds to replication origins. This complex is responsible for the major acetylation of histone H4 on lysine 5, 8, and 12. Knockdown of *HBO1* or *ING5* causes a decrease in DNA synthesis and affects progression through S phase. In both *Xenopus laevis* and in

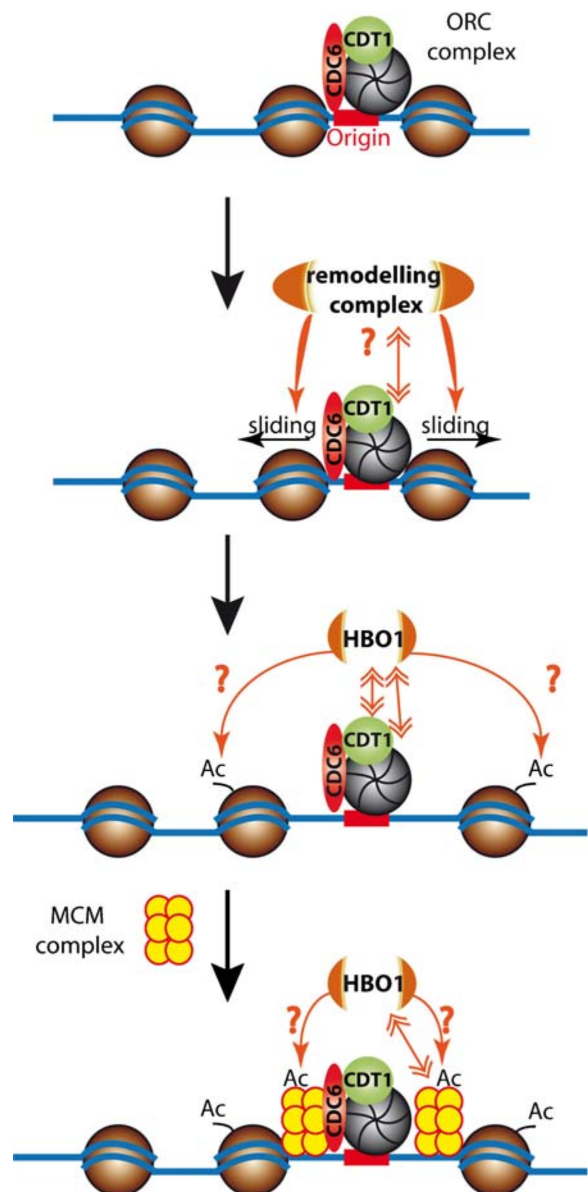

Fig. 2 Chromatin remodeling and origin recognition. Chromatin remodeling complexes recruited at DNA replication origins through interactions with pre-RC proteins might permit acetylation of surrounding nucleosomes by HAT complexes and a change in nucleosome position relative to the DNA sequence. This might facilitate MCM recruitment onto DNA replication origins. HBO1 could also bind to MCM2 and acetylate one or more subunits of the MCM complex

human cells, *HBO1* depletion inhibits the recruitment of MCM complex to chromatin (Iizuka et al. 2006; Wu and Liu 2008). Recent findings in mammalian cells link HBO1 to Cdt1 (a crucial pre-RC component) as a co-activator of replication licensing (Miotto and Struhl 2008). Moreover, binding of HBO1 to the Kaposi's sarcoma-associated herpes virus terminal repeats (the origin of viral DNA replication) contributes to replication of the viral genome (Stedman et al. 2004). Together, these findings suggest that HBO1, via its ability to acetylate H4 on lysine 5, 8, and 12, is required for pre-RC formation at DNA replication origins, but whether acetylation of histones is a general feature of DNA replication origins remains to be demonstrated (Cadoret et al. 2008; Dazy et al. 2006; Gregoire et al. 2006).

Higher levels of chromatin organization

Loops, matrix, and DNA replication origins

The coordinated activation of DNA replication origins takes place in specific nuclear structures called DNA replication foci (Fig. 3). When short BrdUTP or biotin-dUTP pulses are performed during S phase, several hundred foci can be revealed by indirect immunodetection of the labeled precursor analogues (Jackson 1995; Jackson and Pombo 1998; Ma et al. 1998; Nakamura et al. 1986). Similar structures have been described in eukaryotes ranging from yeast to human cells. The DNA foci that are labeled by this approach appear as stable units of chromosome structure which can be visualized as discrete units in individual chromosome territories (Berezney et al. 2000). They are believed to be organized as clusters of chromatin loops that can be detected when most of the chromatin proteins are removed by extracting nuclei with high salt or with lithium 3,5-diiodosalicylate. A residual nuclear structure consisting of loop domains anchored to a nuclear skeleton is then observed (reviewed in Gilbert and Gasser 2006). This residual network is often called the nuclear matrix or scaffold and has been found in both animal and plant nuclei. This architecture of loop domains has been suggested to play an important role in organizing chromosomes for replication (Vogelstein et al. 1980). Despite an abundant literature, this finding remains controversial, although a similar nucleoskeleton was also observed using physiological extraction conditions (Jackson and Cook 1986).

Genomic DNA contacts the nuclear matrix at specific sites called matrix attachment regions (MARs or SARs for scaffold attachment regions) that are relatively resistant to DNAse digestion of extracted nuclei. MARs are 0.5- to 3-kb regions often found at the 5′ of genes (Glazko et al. 2003). The specific DNA/matrix contacts yield inter-MAR loops ranging from 20 to 200 kb (Jackson et al. 1990), which vary depending on the cell cycle and cell identity. Matrix attachment sites are also associated with binding sites for topoisomerase II (Razin et al. 1991), an enzyme which is essential for loop remodeling. Recently, the first genome-wide studies to localize MARs were performed in human cells (Linnemann et al. 2007; Linnemann et al. 2009). As expected, a significant proportion of MARs were found to be associated with expressed genes. DNA replication origins also follow the same trend (unpublished data). However, it is clear that strong bias was observed depending on the method used to purify matrices, indicating that their preparation is still a sensitive aspect of experimental design.

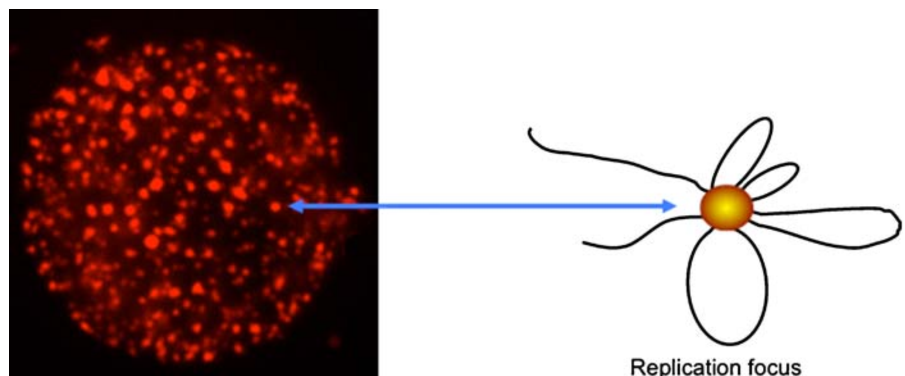

Fig. 3 DNA replication foci and clusters of replication origins. Replication foci were identified by biotin-dUTP pulse during DNA synthesis in *Xenopus* egg extract. A single nucleus is shown. Replication foci are thought to occur by association of several replicons that are synchronously activated in each focus

Numerous observations suggest a functional link between MARs and origins of DNA replication. First, many MARs are associated with origins of DNA replication. Indeed, MARs have been found at or very close to the chicken *lysozyme* DNA replication origin (Phi and Straetling 1988), the *DHFR* origins β and β′ (Dijkwel and Hamlin 1988), the *lamin B2* origin (Lagarkova et al. 1998), and the c-*myc* origin (Girard-Reydet et al. 2004). Interestingly, origins/MARs association is a conserved feature (Girard-Reydet et al. 2004). Secondly, MAR-associated sequences are enriched in replication intermediates (Dijkwel et al. 1991). Lastly, the addition of MAR sequences to plasmids enhances their episomal replication (Papapetrou et al. 2006). MARs, together with DNA replication origin sequences, allow propagation of plasmid DNA without the use of selection agents (Jenke et al. 2004). In addition, MARs enhance stable transgene expression, possibly through their chromatin-organizing activity (Harraghy et al. 2008).

What is the link between MARs and DNA replication origins? By bringing specific DNA sequences to the matrix, MARs could facilitate the formation of replication initiation complexes. Also, MARs could link several DNA replication origins together at the nuclear matrix, resulting in clustered origins and thus facilitating their coordinated firing (Eivazova et al. 2009). MARs are also AT-rich sequences (Mirkovitch et al. 1984), and such AT richness could stimulate DNA replication origin activation because of its unique DNA unwinding properties.

Programming DNA replication origins and chromosome architecture

Several recent studies have revived the links between DNA loops, replicons, and DNA replication origins. A compelling correlation between replicons and chromatin loops was initially reported by Buongiorno-Nardelli et al. (1982) who showed that the size of replicons was identical to the size of DNA loops in several animal and plant species, as well as during development in *Xenopus*. Pioneering experiments in *Xenopus* showed that a nucleus from a differentiated cell could be reprogrammed after transplantation into an enucleated egg (Gurdon 1962). However, the success of such cloning experiments was low (3 to 5%) and still remains low (under 10%) whatever animal species is used. It has been postulated that one of the main reasons for this low efficiency is that the genome from differentiated cells had to accommodate the rapid DNA replication cycles that are characteristic of early development.

When nuclei from differentiated cells are introduced in *Xenopus* egg extracts competent for S phase, they replicate rather slowly and with inter-origin spacing similar to that seen in somatic cells (90 kbp). This

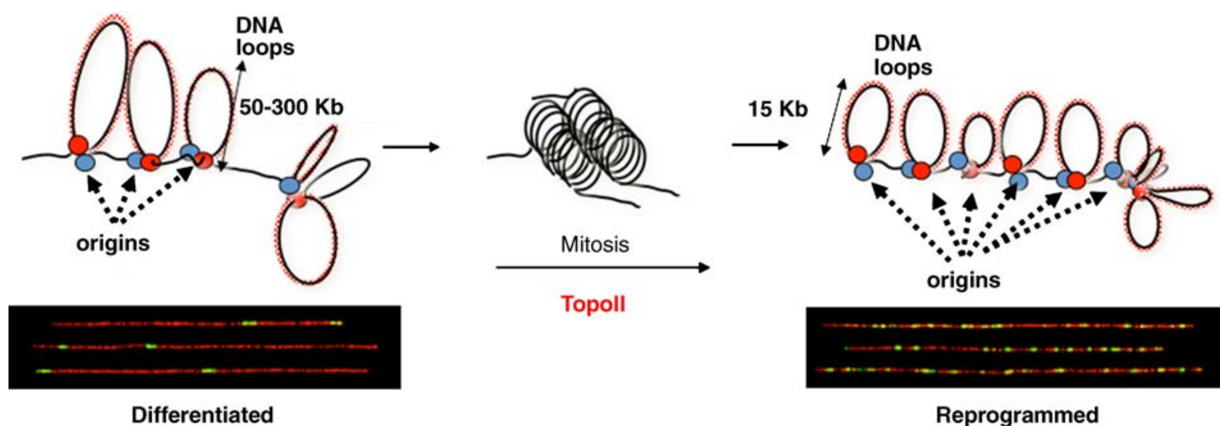

Fig. 4 Reprogramming of DNA replication origins during mitosis. Mitosis can reset DNA replication origins and adapt the replication of chromosomes to a new cell program. The organization of chromatin loops and the density of DNA replication origins of a differentiated nucleus can be fully remodeled by passing through mitosis in an egg extract. This process is topoisomerase II-dependent. DNA replication origins are thus set at short intervals (10–15 kbp), as required for the rapid rounds of DNA replication that occur during early stages of *Xenopus* development

contrasts with the much shorter inter-origin spacing characteristic of early *Xenopus* embryos (~15 kbp) and also with the DNA replication origin spacing in sperm nuclei incubated with *Xenopus* egg extracts. However, when nuclei from differentiated, somatic cells were conditioned in mitotic egg extracts before transplantation, they gained the short inter-origin spacing typical of S phase induction. Strikingly, replicons were reprogrammed by passing through mitosis first. A similar observation was later made in mammalian cells, confirming this result (Courbet et al. 2008). Specifically, in these cells, a reduction in the concentration of replication precursor pools led to a decrease of fork speed and was associated with an increase in number of active replication origins. Interestingly, as previously observed in *Xenopus*, passing through mitosis was essential for fixing origin usage, and shorter replicons were seen in the following S phase even when the precursor pools were restored.

These observations imply that an event occurring at mitosis is important to allow the selection of DNA replication origins that can be used in the next cell cycle (Fig. 4). This step appears crucial for reprogramming nuclei during early development, and it was indeed shown that the transfer of mouse somatic nuclei in mitotic zygotes improves reprogramming in mouse as well (Egli et al. 2007). What is the mechanism responsible for this phenomenon? A similar analysis on the loop size in *Xenopus* led to the conclusion that exposure of differentiated nuclei to mitotic conditions in *Xenopus* egg extracts induces a global change in their chromosomal architecture. Specifically, when erythrocyte nuclei were exposed to such extracts, their average DNA loop size fell from 97 to 15 kpb. A similar correlation between replicon size and loop size was observed in mammalian cells (Courbet et al. 2008). In *Xenopus*, remodeling of both the loop size and of the DNA replication origin spacing is controlled by topoisomerase II (Lemaitre et al. 2005). This is in agreement with the observation that topoisomerase II is an enzyme associated with the nuclear matrix (Earnshaw and Heck 1985). Reprogramming of the distribution of DNA replication origins correlates with ORC recruitment to chromatin, which is also topoisomerase II-dependent (Lemaitre et al. 2005).

Together, these data from two different animal species indicate that mitosis is a crucial step for programming the chromosomal architecture that is used to define the regulation of DNA synthesis during the following S phase. Events that occur during G–S period of the cell cycle, where the distribution of potential origins is defined (Wu and Gilbert 1996), are thus also dependent on previous mitotic events. Although chromosomal loops and loop anchors are still poorly defined biochemically, these data suggest that chromosome architecture plays a predominant role in the regulation of DNA replication origin localization and activation. How ORC, the main origin recognition protein, recognizes this architecture is still unknown. Over recent years, several new members of the replication initiation complex have been identified. Unraveling how these complexes interact with eukaryotic chromatin might help to explain how DNA loops and chromatin domains are formed and if/how the structure of replication domains participates in gene expression and the control of cell identity.

Acknowledgments We would like to thank E. Andermarcher for critical reading of this manuscript. CC was supported by the FRM and PC was supported by the FRM and ARC. Our laboratory is supported by the European Research Council, by the ANR, the “Association pour la Recherche contre le Cancer” and the “Ligue Nationale contre le Cancer”.

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