Minireview

Split Decision: What Happens to Nucleosomes during DNA Replication?*

Anthony T. Annunziato‡

*From the Biology Department, Boston College,
Chestnut Hill, Massachusetts 02467*

The heritability of cell-specific gene regulation argues that chromatin structures must be propagated across cell generations (1–5). A corollary of this hypothesis is that specific histone-DNA interactions are reestablished during chromatin synthesis, and in fact nucleosomes are rapidly generated on newly replicated DNA (6–8). The histones required for nascent nucleosomes are derived from two sources: parental histones (dispersively segregated to both arms of the fork) and new histones, especially new H3/H4, that are deposited during *de novo* nucleosome assembly. (Note: new H2A/H2B dimers are not uniquely targeted to nascent DNA but are also deposited onto non-replicating chromatin (9, 10).) Replication-coupled nucleosome assembly occurs in a stepwise fashion; first histones H3 and H4 are deposited and then H2A and H2B (11, 12). The deposition of H3/H4 onto new DNA is mediated by the assembly factor CAF-1; the H3/H4-escort protein Asf1 appears to assist CAF-1 in this process (8, 13–15).

Not all histone synthesis occurs in conjunction with DNA replication. Distinct non-allelic histone variants are synthesized at basal levels throughout the cell cycle and can be incorporated into chromatin in a replication-independent manner during G_1 and G_2 (16–19). These "basal histone variants" are found in virtually all eukaryotes and contain conserved amino acid substitutions that differentiate them from replication-dependent subtypes (20). For example, in mammals the replication-independent variant H3.3 differs by only 4–5 amino acids from the major replication-dependent H3 isoform, H3.1 (20, 21). There is evidence that H3.3 is incorporated into chromatin during transcription (22, 23). Moreover, in a recent paper by Tagami *et al.* (24) it was shown that the replication-independent deposition of H3.3 into chromatin is mediated by a specialized assembly factor, HIRA, in agreement with previous findings that HIRA can mediate replication-independent nucleosome assembly (25). Thus, there is evidence that replication-dependent and replication-independent histone deposition pathways utilize two separate assembly factors, CAF-1 and HIRA, respectively (15, 26, 27).

Newly synthesized H3 and H4 are associated with each other prior to their assembly into chromatin (reviewed in Ref. 8) (28–30). Until recently there has been little evidence to indicate whether the coordinate deposition of H3 and H4 occurs in the form of dimers or tetramers. However, in the aforementioned paper by Tagami *et al.* (24) it was shown that purified chromatin assembly complexes containing either CAF-1 or HIRA are likely to contain H3/H4 dimers, not tetramers. The observation of pre-deposition complexes containing H3/H4 dimers has prompted the rethinking of how histones are assembled onto DNA (31). It also has sparked new interest in the question of how parental, pre-fork histones are distributed during replication. Extrapolating from their findings, one of the models proposed by Tagami *et al.* (24) is that parental H3/H4 tetramers dissociate into heterotypic dimers, which are

segregated to both arms of the replication fork (Fig. 1). It was further proposed that segregated dimers are then converted to tetramers by the deposition of newly synthesized H3/H4 dimers, as mediated by CAF-1 (24).

Other chromatin assembly models were also proposed by Tagami *et al.* (24), including the cooperative action of two CAF-1 complexes (each carrying one nascent H3/H4 dimer). Nevertheless, questions surrounding the "splitting tetramer" model have refocused attention on the manner in which old histones are segregated to new DNA. There is a large and varied literature on this topic, embodying experiments that reach back to some of the first analyses of chromatin replication and assembly (reviewed in Ref. 6). In the following article, experiments dealing with the fate of pre-replicative nucleosomes are examined in an effort to better evaluate possible models of chromatin replication and assembly *in vivo*.

Histone Segregation during Chromatin Replication

Investigations of the behavior of parental histones during DNA synthesis have historically addressed two questions. 1) Are "old" histones transferred to both arms of the replication fork? 2) Do parental histone complexes remain intact during replication, and if so, what is the nature of these complexes? After a period of considerable debate, the first question was ultimately resolved when several laboratories provided evidence that parental histones are dispersively segregated to both sides of the fork (reviewed in Ref. 6). Thus pre-existing histones, and potentially the modifications they possess, can be "inherited" by both copies of a newly replicated chromatin region, as previously shown for histone acetylation (32).

Early studies of the composition of "old" histone complexes that are transferred to newly replicated DNA grew out of the analysis of histone segregation. To exclusively detect parental histones on new DNA, it is necessary to prevent the deposition of newly synthesized histones. This can be done in cycling cells through the use of protein synthesis inhibitors such as cycloheximide or puromycin. When protein synthesis is inhibited, DNA replication continues for a brief period during which parental histones are continually transferred to the growing nascent duplexes. By radiolabeling new DNA *in vivo* in the presence of cycloheximide and subsequently digesting nascent chromatin with micrococcal nuclease, it was independently demonstrated in the laboratories of Weintraub (33) and Seale (34) that nucleosomal arrays with regular spacing were present on approximately half of the DNA replicated in the absence of *de novo* nucleosome assembly. Because the digestion products had the characteristics of complete nucleosomes (not half-nucleosomes), it was generally concluded that histone octamers are segregated to new DNA either as intact units or as rapidly reassembled substructures. No evidence for the semi-conservative distribution of split nucleosomes to new DNA was observed.

The presence of typical nucleosomal ladders on "cycloheximide chromatin" also led early investigators to conclude (erroneously) that parental histones are segregated exclusively to one side of the fork (perhaps with a preference for either the leading or lagging strand). Subsequent analyses demonstrated that pre-existing histone octamers are segregated in clusters of varying size to both daughter DNA molecules (35–38). It was further shown that segregated parental mononucleosomes were indistinguishable from the mononucleosomes of "bulk" chromatin, as determined by sedimentation characteristics and electrophoretic mobility (36, 39). Experiments into the mode of histone segregation were also performed in cell-free systems through the study of chromatin replication in isolated nuclei (40) or using purified SV40 minichromosomes (36, 41, 42). During replication under these conditions, histone segregation still occurs, but there are no new histones available for *de novo* nucleosome assembly. Results from these studies were fully consistent with those performed on chromatin replicated in the presence of cycloheximide in living cells. An alternative approach to the question of histone segregation

A Tetramer Conserved

B Tetramer Splits

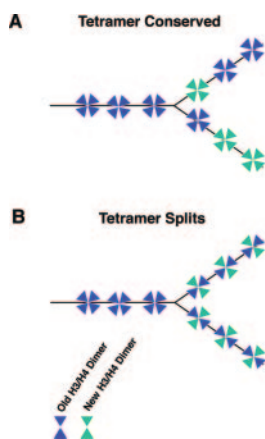Old H3/H4 Dimer   New H3/H4 Dimer

F_IG. 1. **Models of H3/H4 segregation during chromatin replication.** For *A* and *B*, old H3/H4 dimers are *blue*; new H3/H4 dimers are *green*. *A*, old H3/H4 tetramers remain intact during replication; newly assembled tetramers exclusively contain new H3/H4. *B*, old H3/H4 tetramers split into heterotypic dimers during replication; new tetramers are assembled from both new and old H3/H4 dimers. Only histones H3 and H4 are shown in the figure.

involves electron microscopic analysis of replicating chromatin. The elegant electron microscopy studies of McKnight and Miller (43) had shown that nucleosomes form rapidly on both sides of the fork during normal replication and assembly. To selectively determine the behavior of parental histones during replication, Crémisi *et al.* (44) analyzed polyoma virus minichromosomes that had replicated in the presence of the protein synthesis inhibitor puromycin. Normal polyoma minichromosomes contain ~21 nucleosomes on a circular DNA template. Following replication in virus-infected CV1 cells under control conditions, polyoma minichromosomes contained typical nucleosome number and spacing. After replication in puromycin, the replication products contained on average only ~11 "beads" per DNA molecule, with 65% of the molecules having between 11 and 15 nucleosomal structures. The segregated beads had a normal ultrastructure and appeared to be clustered; no half-nucleosomes were observed (44). Virtually identical results were later obtained by Sogo *et al.* (45) through psoralen cross-linking of SV40 minichromosomes replicated in cycloheximide. Thus the random segregation of groups of histone octamers, initially observed through biochemical analysis, was also supported by direct electron microscopic observation.

Stability of the H3/H4 Tetramer in Vitro and in Vivo

A factor that bears upon the potential splitting of H3/H4 tetramers during DNA replication is the stability of histone-histone interactions. One means of addressing tetramer stability involves the study of histone complexes that form *in vitro* in the absence of DNA. At conditions close to physiological ionic strength and pH, purified H3/H4 dimers and tetramers are in equilibrium with the tetramer tending to be predominant (46). By altering the solvent conditions, the relative proportions of tetramers and dimers can be changed (46–48); tetramers can also be separated into heterotypic dimers by elevated temperatures or by denaturing agents such as guanidine HCl (47, 48). Although many details of these histone solution studies differ, largely because of variations in experimental conditions and design, it seems clear that *in vitro* H3/H4 tetramers can split at the H3-H3 interface to yield free H3/H4 dimers. Yet the question remains: how stable is the H3/H4 tetramer *in vivo*?

Prior *et al.* (49) analyzed the long term stability of nucleosomal H3-H3 interactions *in vivo* in the slime mold *Physarum*. This organism has the well characterized ability to take up exogenous proteins placed on its surface and to incorporate the intact proteins into cellular structures. In their studies, Prior *et al.* (49) used the cysteine-specific, fluorescent reagent iodoacetoxypyrene, which forms a covalent bond exclusively at C-110 of H3, to monitor tetramer assembly and (possible) disruption. The emission spectrum of monomeric pyrene appears blue; however, when two pyrenes are in close proximity, an excimer complex that emits green light is formed. Because C-110 of H3 lies at the H3-H3 interface in the H3/H4 tetramer, fluorescent derivatives of H3 can be used as probes of tet-

ramer integrity. As expected, nucleosomes reconstituted with pyrene-labeled H3 (AP-H3) emitted green fluorescence. Further control experiments by Prior *et al.* (49) demonstrated that AP-H3 applied to *Physarum* microplasmodia could be imported into the nucleus and assembled into nucleosomes.

When first taken up by cells, AP-H3 emitted blue fluorescence in the *Physarum* cytoplasm. Blue fluorescence was subsequently seen in nuclei, consistent with the import of either unpartnered H3 or H3/H4 dimers. With time, blue fluorescence sharply declined, and green fluorescence in nuclei and nucleosomes was detected. Nearly 80% of the blue cytoplasmic fluorescence subsequently appeared as green excimer fluorescence in nucleosomes, a consequence of the close apposition of two AP-H3 molecules in newly deposited H3/H4 tetramers. Importantly, during a prolonged 90-h chase period in which unlabeled histones were added to the microplasmodia, green fluorescence remained detectable, even after five rounds of DNA replication. Although the intensity of green fluorescence slowly declined (presumably because of the dilution of AP-H3 nucleosomes every generation), blue fluorescence did not return. The persistence of green fluorescence thus demonstrated that the excimer complex was conserved over several generations, consistent with the long term stability of individual H3/H4 tetramers during multiple rounds of replication *in vivo*.

Ten years after the experiments of Prior *et al.* (49), Jackson (50) reexamined the stability of H3/H4 tetramers in cycling mammalian cells, using density labeling techniques. Cells were grown for several generations in dense amino acids (containing the heavy isotopes ^{13}C and ^{15}N) in the presence of radiolabeled arginine and lysine. Cells were then shifted to light medium containing normal amino acids for over three generations (48-h "chase"). Histone octamers in isolated nuclei were then cross-linked with formaldehyde at pH 9.1, a treatment that cross-links histones to each other but not to DNA (51). Cross-linked octamers were then extracted and subjected to density equilibrium centrifugation in cesium formate to measure the relative densities of pulsed and chased octamers. Even after three generations in normal amino acids, dense (radiolabeled) H3/H4 remained in octamers that were predominantly half-dense. In contrast, labeled H2A/H2B dimers were widely distributed and mostly found in octamers with densities between half-dense and normal.

Jackson (50) interpreted the presence of labeled (dense) H3/H4 in half-dense octamers to be the result of one fully dense tetramer in association with two normal ("light") H2A/H2B dimers. If dense tetramers had split into H3/H4 dimers during replication, hybrid (dense-light) tetramers would have been generated after one round of nucleosome assembly in the presence of normal amino acids. In subsequent generations, octamers containing labeled H3/H4 would have densities ranging from three-fourths dense to one-fourth dense, depending on the relative proportion of H2A/H2B with normal density (Fig. 2). Given the demonstrated exchange of H2A/H2B *in vivo* (reviewed in Ref. 8), one would predict that after three cell divisions most octamers containing labeled H3/H4 would be only one-fourth dense, as normal histones become predominant (Fig. 2). Jackson (50) did not observe this. Instead, labeled H3/H4 largely remained in octamers that were half-dense, whereas labeled H2A/H2B were found in significantly lighter octamers. It was therefore concluded that, at least in most cases, parental H3/H4 tetramers do not dissociate into dimers during DNA synthesis.

By density labeling new histones, Yamasu and Senshu (52) also examined the stability of H3/H4 tetramers during replication. To deplete H2A and H2B and leave H3/H4 tetramers bound to DNA, purified mononucleosomes were sedimented through sucrose gradients containing 4 M urea and 0.3 M NaCl, yielding particles containing only H3 and H4. It was observed in control experiments (not presented) that only H1, H2A, H2B, and non-histone proteins were released from the depleted nucleosomes and that the resulting particles had a histone:DNA ratio of 0.56, consistent with H3/H4 tetramers remaining bound to DNA. A similar histone:DNA ratio (0.48) had been observed previously by Woodcock and Frado (53), who used 6 M urea and 0.2 M NaCl to deplete H2A/H2B from mononucleosomes.

Yamasu and Senshu (52) then resolved density-labeled, H3/H4 subnucleosomes by rate zonal centrifugation. After growing cells for up to 15 h (one replication cycle) in dense amino acids, H3/H4
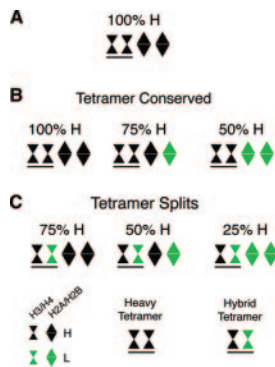
FIG. 2. **Predicted composition of new histone octamers containing radiolabeled H3/H4.** For *A*, *B*, and *C*, heavy radioactive histones are *black* and unlabeled histones are *green*; H3/H4 dimers are represented by *hourglasses* and H2A/H2B dimers by *diamonds*. The percent heavy histone (*H*) is given above each octamer species. *A*, after growing cells for 40 h in heavy amino acids (50), ~90% of all histone octamers will be 100% heavy. *B*, possible classes of histone octamers after three rounds of replication in normal amino acids if H3/H4 tetramers are conserved; in this case histone octamers will be ≥50% heavy. *C*, possible classes of histone octamers after three rounds of replication in normal amino acids if H3/H4 tetramers split into heterotypic dimers; in this case histone octamers will be ≥25% heavy. Because new octamers are non-conservatively assembled (a consequence of H2A/H2B exchange), in all cases heavy radioactive H3/H4 will tend to be found in the *lightest* possible octamers after three rounds of replication in normal amino acids. For *A*, *B*, and *C*, only octamers containing radiolabeled H3/H4 are depicted.

subnucleosomal particles still remained in two distinct classes: heavy and normal (*i.e.* new and old). The authors therefore concluded that newly assembled H3/H4 tetramers contain only newly synthesized H3 and H4 (52), which would be inconsistent with parental tetramer splitting during chromatin replication. Additional experiments then confirmed the stability of radiolabeled old H3/H4 tetramers through a single round of replication (52).

Nucleosome Disruption during DNA Replication

In a series of papers that span almost two decades, Sogo and colleagues (45) have used psoralen cross-linking and electron microscopy to examine nucleosome structural transitions during DNA replication. The photocross-linking of DNA in the presence of psoralen (4,5′,8-trimethylpsoralen) causes covalent joining of the base-paired DNA strands. Notably, when chromatin fibers are treated with psoralen, only the linker DNA is cross-linked, thereby preventing DNA melting; DNA in nucleosomes remains unaffected. When DNA from psoralen-cross-linked SV40 chromatin is denatured and spread on a water surface and then viewed in the electron microscope, single-stranded (ss)[1] DNA "bubbles" corresponding to individual nucleosomes (~140–180 nt in length) are observed (45). The nucleosomal bubbles are connected by short cross-linked segments of double-stranded linker DNA.

An examination of psoralen-cross-linked SV40 chromatin that had replicated in infected cells in the presence of cycloheximide (*i.e.* in the absence of new histone deposition) revealed typical nucleosomal structures on the new DNA, not the smaller bubbles predicted for H3/H4 dimers or heterotypic tetramers (45). In contrast, SV40 minichromosomes replicated in a cell-free system, in the absence of concurrent nucleosome assembly, yielded two sizes of ss bubbles on new DNA (~180 and ~90 nt). These were taken to represent histone octamers and H3/H4 tetramers, respectively (54). The relative proportions of these structures depended on the method of chromatin isolation or the presence of a 5–10-fold molar excess of competitor DNA during replication (54). When the replication reaction was supplemented with excess free H2A/H2B, the 90-nt ss bubbles were converted to bubbles of 180 nt. The authors, therefore, concluded that during replication parental H3/H4 tetramers are segregated to new DNA prior to H2A/H2B dimers to produce segregated octamers containing only old H3/H4.

The only means of determining the structure of nucleosomes *ahead* of the replication fork is by electron microscopy. Through psoralen cross-linking of chromatin under conditions that "moderately destabilize" nucleosomes, Sogo and colleagues (55) examined the fate of prefork nucleosomes on SV40 chromatin replicated *in vivo*. By comparing results obtained with replicating SV40 chromatin to nucleosomal structures seen under defined conditions (including H1 depletion and elevated pH), it was concluded that the first two nucleosomes ahead of the fork are destabilized, each to a different degree. Nucleosomes partially invaded by the replication fork appeared to lack histone H1 and possibly one or both H2A/H2B dimers (at least in some cases); when cross-linked *in vivo*, most of these yielded ss bubbles of 70 nt (although the size distribution was very broad). The penultimate prefork nucleosome was H1-depleted but otherwise intact. Nucleosomes immediately behind the fork were normal and appeared to have regained H1, consistent with an earlier biochemical analysis of chromatin replication in HeLa cells (56).

To test the *requirement* for prefork nucleosome dissolution during chromatin replication, Vestner *et al.* (57) examined replicating SV40 minichromosomes that had been reconstituted by means of salt dialysis with histone octamers that had previously been cross-linked using dimethyl suberimidate. SV40 templates containing cross-linked octamers were completely replicated *in vitro* (although the replication rate was slowed). Significantly, the cross-linked octamers were transferred to the daughter strands normally, demonstrating that octamers need not be disassembled to allow passage of the replication fork.

Do "Half-nucleosomes" Exist?

Over the years there have been intriguing reports of chromatin structures with properties that suggest half-nucleosomal particles. Whether any of these structures in fact represent heterotypic histone tetramers bound to DNA remains unclear. In high resolution indirect end-labeling experiments, Lee and Garrard (58) showed that the 3′-end of the yeast *HSP82* gene was cleaved at ~80-bp intervals by DNase I, both before and after heat shock. This "half-nucleosomal" cleavage was not observed on the 5′-half of the *HSP82* gene or on naked DNA. (A similar DNase I cutting pattern at ~100-bp intervals had previously been observed on the *Drosophila hsp26* gene (59).) Interestingly, the 80-bp repeat could not be detected by micrococcal nuclease digestion, which yielded a typical ~160-bp ladder, both before and after heat shock. The authors postulated that a moving RNA polymerase could cause nucleosomes on the 3′-end of the *HSP82* gene to adopt an altered configuration, thus permitting DNase I to cleave at the nucleosome dyad axis (58). Notably, the results using micrococcal nuclease argue strongly for the maintenance of either H3/H4 *tetramers* or complete histone octamers along the entire *HSP82* gene (58). This would be consistent with reports of "unfolded" nucleosomes on active genes, which retain a normal complement of mononucleosomal DNA (60–63). It has been proposed that the extended nucleosomal conformation may reflect tetramer unfolding at the H3-H3 interface, as judged by the increased accessibility of the sulfhydryl groups of H3 in the unfolded particles (61, 63).

Electron microscopy has also provided evidence for the generation of "half-nucleosomal" structures, at least *in vitro*. When SV40 minichromosomes were diluted into very low ionic strength buffer at 0 °C, the number of beads associated with the circular DNA template was doubled, from 20 ± 2, to ~45 (average) (64). The mean diameter of the new and more numerous particles decreased significantly, from ~125 to ~93 Å; however, the protein composition of the putative half-nucleosomes was not determined. Although biophysical studies have also provided evidence for nucleosome unfolding under conditions of very low ionic strength (Refs. 65 and 66, and references cited therein), the formation of heterotypic tetramers or H3/H4 dimers has not been documented. It is worth noting that such experiments have probed nucleosome stability under conditions that are far from physiological. Nevertheless, they may provide clues about the forces that hold nucleosomes together.

Concluding Remarks

It must be concluded that there is as yet no compelling evidence for H3/H4 dimers (apart from those occurring in tetramers) in association with chromatin DNA. On the other hand, it could be argued that H3/H4 dimers are only stable when complexed with assembly escorts or other factors and are therefore so transient as

---

[1] The abbreviations used are: ss, single-stranded; nt, nucleotide(s).

to be undetectable as separate entities when present in chromatin.

To date, studies of chromatin replication have provided overwhelming evidence for the segregation of parental H3/H4 tetramers and histone octamers to newly replicated DNA, as opposed to H3/H4 dimers or half-nucleosomes. Although the mechanism of histone segregation remains unknown and may involve the transient dissociation of H2A/H2B dimers from the nucleosome, it seems safe to conclude that in the vast majority of cases H3/H4 tetramers do not split during chromatin replication. An important caveat to this statement is that most studies of histone segregation have relied on the elimination of new histone deposition and *de novo* nucleosome assembly so that only old histones could be detected on new DNA. Experiments performed under these conditions may skew the results toward the conservation of octamers during chromatin replication. However, investigations of tetramer assembly and stability that rely on density labeling or photolabeling of histones are performed under essentially native conditions. In all such cases, the conservative assembly of new H3/H4 tetramers from entirely new histones has been observed. Nevertheless, because the resolution of cross-linked octamers is not absolute in these experiments, it may be that defined classes of nucleosomes can "split" under certain circumstances (as discussed in Ref. 31). Given the accumulated evidence against tetramer splitting, it seems likely that two nascent H3/H4 dimers come together to assemble new tetramers *in vivo*. Perhaps the H3/H4 escort Asf1, which facilitates the activity of CAF-1 (67–69), provides the second dimer that is required for *de novo* nucleosome assembly (24).

The evidence for an epigenetic histone code raises the question as to whether the code is heritable, and if so, how (3–5). H3/H4 tetramer splitting at the replication fork would offer a direct method for the transfer of matching histone modifications to both nascent chromatin fibers (assuming that both H3/H4 dimers carry the same marks). However, tetramer stability need not preclude the inheritance of histone modification patterns provided that pre-existing modifications can persist during the replication process (as has already been demonstrated for histone acetylation (32)). In this case, one can envisage that the bromodomains, chromo domains, etc. of histone-modifying enzymes and their associated proteins (70, 71) would recognize their cognate modifications on segregated parental histones, thereby effecting the propagation of specific modifications to the surrounding nascent chromatin (3, 72, 73). Each round of replication would thus provide opportunities for preserving (or erasing) histone modification patterns, depending on the availability of the modifying enzymes.

REFERENCES

1. van Holde, K. E. (1988) in *Chromatin* (Rich, A., ed) Springer Series in Molecular Biology, Springer-Verlag, New York
2. Wolffe, A. P. (1999) *Chromatin: Structure and Function*, 3rd Ed., Academic Press, San Diego, CA
3. Strahl, B. D., and Allis, C. D. (2000) *Nature* **403,** 41–45
4. Jenuwein, T., and Allis, C. D. (2001) *Science* **293,** 1074–1080
5. Turner, B. M. (2000) *Bioessays* **22,** 836–845
6. Annunziato, A. T. (1995) in *The Nucleus* (Wolffe, A. P., ed) Vol. 1, pp. 31–55, JAI Press, Greenwich, CT
7. Krude, T. (1999) *Eur. J. Biochem.* **263,** 1–5
8. Annunziato, A. T., and Hansen, J. C. (2000) *Gene Expr.* **9,** 37–61
9. Jackson, V., and Chalkley, R. (1981) *Cell* **23,** 121–134
10. Annunziato, A. T., Schindler, R. K., Riggs, M. G., and Seale, R. L. (1982) *J. Biol. Chem.* **257,** 8507–8515
11. Smith, S., and Stillman, B. (1991) *EMBO J.* **10,** 971–980
12. Almouzni, G., Clark, D. J., Méchali, M., and Wolffe, A. P. (1990) *Nucleic Acids Res.* **18,** 5767–5774
13. Kaufman, P. D. (1996) *Cur. Opin. Biol.* **8,** 369–373
14. Tyler, J. K. (2002) *Eur. J. Biochem.* **269,** 2268–2274
15. Loyola, A., and Almouzni, G. (2004) *Biochim. Biophys. Acta Gene Struct. Express.* **1677,** 3–11
16. Wu, R. S., and Bonner, W. M. (1981) *Cell* **27,** 321–330
17. Wu, R. S., Tsai, S., and Bonner, W. M. (1982) *Cell* **31,** 367–374
18. Jackson, V., and Chalkley, R. (1985) *Biochemistry* **24,** 6921–6930
19. Thiriet, C., and Hayes, J. J. (2001) *Gene Dev.* **15,** 2048–2053
20. Franklin, S. G., and Zweidler, A. (1977) *Nature* **266,** 273–275
21. Hraba-Renevey, S., and Kress, M. (1989) *Nucleic Acids Res.* **17,** 2449–2461
22. Ahmad, K., and Henikoff, S. (2002) *Mol. Cell* **9,** 1191–1200
23. McKittrick, E., Gaften, P. R., Ahmad, K., and Henikoff, S. (2004) *Proc. Natl. Acad. Sci. U. S. A.* **101,** 1525–1530
24. Tagami, H., Ray-Gallet, D., Almouzni, G., and Nakatani, Y. (2004) *Cell* **116,** 51–61
25. Ray-Gallet, D., Quivy, J. P., Scamps, C., Martini, E. M. D., Lipinski, M., and Almouzni, G. (2002) *Mol. Cell* **9,** 1091–1100
26. Ahmad, K., and Henikoff, S. (2002) *Proc. Natl. Acad. Sci. U. S. A.* **99,** 16477–16484
27. Korber, P., and Hörz, W. (2004) *Cell* **117,** 5–7
28. Perry, C. A., Dadd, C. A., Allis, C. D., and Annunziato, A. T. (1993) *Biochemistry* **32,** 13605–13614
29. Kaufman, P. D., Kobayashi, R., Kessler, N., and Stillman, B. (1995) *Cell* **81,** 1105–1114
30. Verreault, A., Kaufman, P. D., Kobayashi, R., and Stillman, B. (1996) *Cell* **87,** 95–104
31. Henikoff, S., Furuyama, T., and Ahmad, K. (2004) *Trends Genet.* **20,** 320–326
32. Perry, C. A., Allis, C. D., and Annunziato, A. T. (1993) *Biochemistry* **32,** 13615–13623
33. Weintraub, H. (1976) *Cell* **9,** 419–422
34. Seale, R. L. (1976) *Cell* **9,** 423–429
35. Pospelov, V., Russev, G., Vassilev, L., and Tsanev, R. (1982) *J. Mol. Biol.* **156,** 79–91
36. Cusick, M. F., DePamphilis, M. L., and Wassarman, P. M. (1984) *J. Mol. Biol.* **178,** 249–271
37. Annunziato, A. T., and Seale, R. L. (1984) *Nucleic Acids Res.* **12,** 6179–6196
38. Jackson, V., and Chalkley, R. (1985) *Biochemistry* **24,** 6930–6938
39. Annunziato, A. T., and Seale, R. L. (1982) *Biochemistry* **21,** 5431–5438
40. Seale, R. L. (1978) *Proc. Natl. Acad. Sci. U. S. A.* **75,** 2717–2721
41. Krude, T., and Knippers, R. (1991) *Mol. Cell. Biol.* **11,** 6257–6267
42. Randall, S. K., and Kelly, T. J. (1992) *J. Biol. Chem.* **267,** 14259–14265
43. McKnight, S. L., and Miller, O. L., Jr. (1977) *Cell* **12,** 795–804
44. Crémisi, C., Chestier, A., and Yaniv, M. (1978) *Cold Spring Harbor Symp. Quant. Biol.* **42,** 409–416
45. Sogo, J. M., Stahl, H., Koller, T., and Knippers, R. (1986) *J. Mol. Biol.* **189,** 189–204
46. Baxevanis, A. D., Godfrey, J. E., and Moudrianakis, E. N. (1991) *Biochemistry* **30,** 8817–8823
47. Karantza, V., Freire, E., and Moudrianakis, E. N. (1996) *Biochemistry* **35,** 2037–2046
48. Banks, D. D., and Gloss, L. M. (2003) *Biochemistry* **42,** 6827–6839
49. Prior, C. P., Cantor, C. R., Johnson, E. M., and Allfrey, V. G. (1980) *Cell* **20,** 597–608
50. Jackson, V. (1990) *Biochemistry* **29,** 719–731
51. Jackson, V. (1999) *Methods* **17,** 125–139
52. Yamasu, K., and Senshu, T. (1990) *J. Biochem. (Tokyo)* **107,** 15–20
53. Woodcock, C. L., and Frado, L. L. (1978) *Cold Spring Harbor Symp. Quant. Biol.* **42,** 43–55
54. Gruss, C., Wu, J. R., Koller, T., and Sogo, J. M. (1993) *EMBO J.* **12,** 4533–4545
55. Gasser, R., Koller, T., and Sogo, J. M. (1996) *J. Mol. Biol.* **258,** 224–239
56. Annunziato, A. T., Schindler, R. K., Thomas, C. A., Jr., and Seale, R. L. (1981) *J. Biol. Chem.* **256,** 11880–11886
57. Vestner, B., Waldmann, T., and Gruss, C. (2000) *J. Biol. Chem.* **275,** 8190–8195
58. Lee, M. S., and Garrard, W. T. (1991) *EMBO J.* **10,** 607–615
59. Cartwright, I. L., and Elgin, S. C. (1986) *Mol. Cell. Biol.* **6,** 779–791
60. Johnson, E. M., Allfrey, V. G., Bradbury, E. M., and Matthews, H. R. (1978) *Proc. Natl. Acad. Sci. U. S. A.* **75,** 1116–1120
61. Prior, C. P., Cantor, C. R., Johnson, E. M., Littau, V. C., and Allfrey, V. G. (1983) *Cell* **34,** 1033–1042
62. Locklear, L., Jr., Ridsdale, J. A., Bazett-Jones, D. P., and Davie, J. R. (1990) *Nucleic Acids Res.* **18,** 7015–7024
63. Bazett-Jones, D. P., Mendez, E., Czarnota, G. J., Ottensmeyer, F. P., and Allfrey, V. G. (1996) *Nucleic Acids Res.* **24,** 321–329
64. Oudet, P., Spadafora, C., and Chambon, P. (1978) *Cold Spring Harbor Symp. Quant. Biol.* **42,** 301–312
65. Uberbacher, E. C., Ramakrishnan, V., Olins, D. E., and Bunick, G. J. (1983) *Biochemistry* **22,** 4916–4923
66. Brown, D. W., Libertini, L. J., and Small, E. W. (1991) *Biochemistry* **30,** 5293–5303
67. Tyler, J. K., Adams, C. R., Chen, S. R., Kobayashi, R., Kamakaka, R. T., and Kadonaga, J. T. (1999) *Nature* **402,** 555–560
68. Tyler, J. K., Collins, K. A., Prasad-Sinha, J., Amiott, E., Bulger, M., Harte, P. J., Kobayashi, R., and Kadonaga, J. T. (2001) *Mol. Cell. Biol.* **21,** 6574–6584
69. Mello, J. A., Sillje, H. H. W., Roche, D. M. J., Kirschner, D. B., Nigg, E. A., and Almouzni, G. (2002) *EMBO Rep.* **3,** 329–334
70. Loyola, A., and Almouzni, G. (2004) *Trends Cell Biol.* **14,** 279–281
71. Sims, R. J., Nishioka, K., and Reinberg, D. (2003) *Trends Genet.* **19,** 629–639
72. Turner, B. M. (2002) *Cell* **111,** 285–291
73. Felsenfeld, G., and Groudine, M. (2003) *Nature* **421,** 448–453

Split Decision: What Happens to Nucleosomes during DNA Replication?

Anthony T. Annunziato

Access the most updated version of this article at doi: 10.1074/jbc.R400039200

Alerts:

- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 71 references, 17 of which can be accessed free at
http://www.jbc.org/content/280/13/12065.full.html#ref-list-1