

Figure 5. Chaperones and histone dynamics at the replication fork in eukaryotic cells. DNA replication proceeds in an asymmetric manner with continuous synthesis on the leading strand and discontinuous synthesis on the lagging strand. Folding of the two strands in space ensures coupling of replication between the two strands. Two fundamental processes affect the basic unit of chromatin during replication: "nucleosome removal" in front of the replication fork and "nucleosome deposition" on the two daughter strands behind the fork. Disruption of parental nucleosomes into two H2A-H2B dimers and an (H3-H4)<sub>2</sub> tetramer (or two H3-H4 dimers?) and their transfer/recycling onto the newly synthesized daughter strands provides a first source of histones (stages A-D). De novo assembly of new histones (H3-H4 as dimers in complex with histone chaperones) is necessary to restore a full nucleosomal density on the duplicated material (stages E and F). During S phase, this pool is provided by synthesis of replicative histone H3.1 variants in mammals. Although new histones carry a typical diacetylation K5, K12 modification on histone H4 (red "mod"), parental histone PTMs (yellow mod) potentially preserved during transfer can be used as a blueprint to reproduce marks on newly incorporated histones, which could be a means for epigenetic inheritance. How such events function in coordination with progression of the replication fork remains an open issue. The MCM (minichromosome maintenance) 2–7 is thought to mediate DNA unwinding in front of the replication fork. The histone binding activity of Mcm2 could aid the disruption, possibly in conjunction with chromatin remodelers and/or histone modifiers. An interaction with the MCM2-7 complex could favor targeting of the histone chaperones Asfl and FACT (facilitates chromatin transcription), which would handle, respectively, parental H3-H4 (B) and H2A-H2B (A). In addition, Asf1 could pass parental histones onto CAF-1 (C). Because Asf1 interacts with H3-H4 in the form of dimers, parental tetramers (with their own marks) could potentially split and redistribute as dimers in a semiconservative fashion onto daughter strands. The reassembly on nascent DNA, in a stepwise fashion, would proceed via recruitment of CAF-1 to PCNA, which mediates the deposition of H3-H4 dimers provided by Asf1 acting as a histone donor (E). Having Asf1 handling both new and parental histones (C and E) would provide a means to coordinate histone supply with replication fork progression. With dynamics of H2A-H2B being relatively important throughout the cell cycle, it may be that assembly of these histones could simply use the NAP1 histone chaperone for H2A-H2B without a particular need to have a direct connection with the replication fork. NAP1 would bring in new histones H2A-H2B, and possibly old H2A-H2B, made available from transcriptional exchange (C). (Adapted, with permission, from MacAlpine and Almouzni 2013, © Cold Spring Harbor Laboratory Press.)