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The dynamics of eukaryotic replication initiation: origin specificity, licensing, and firing at the single-molecule level.

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Abstract

Eukaryotic replication initiation is highly regulated and dynamic. It begins with the origin recognition complex (ORC) binding **DNA** sites called origins of replication. ORC, together with Cdc6 and Cdt1, mediate pre-replicative complex (pre-RC) assembly by loading a double hexamer of Mcm2-7: the core of the replicative helicase. Here, we use single-molecule imaging to directly visualize Saccharomyces cerevisiae pre-RC assembly and replisome firing in real time. We show that ORC can locate and stably bind origins within large tracts of non-origin **DNA** and that Cdc6 drives ordered pre-RC assembly. We further show that the dynamics of the ORC-Cdc6 interaction dictate Mcm2-7 loading specificity and that Mcm2-7 double hexamers form preferentially at a native origin sequence. Finally, we demonstrate that single Mcm2-7 hexamers propagate bidirectionally, monotonically, and processively as constituents of active replisomes.

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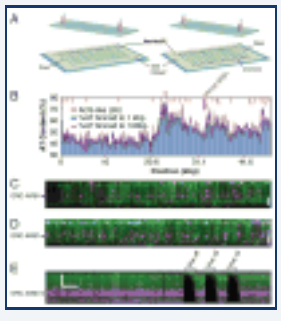
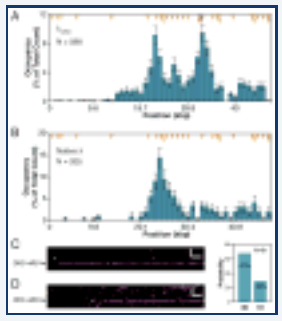
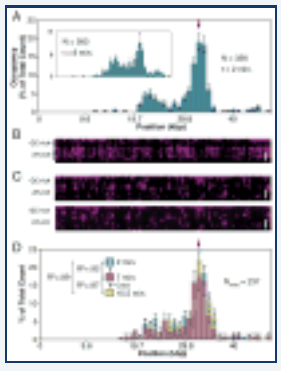
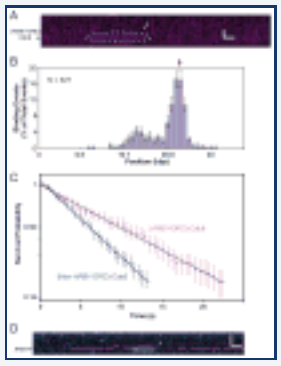
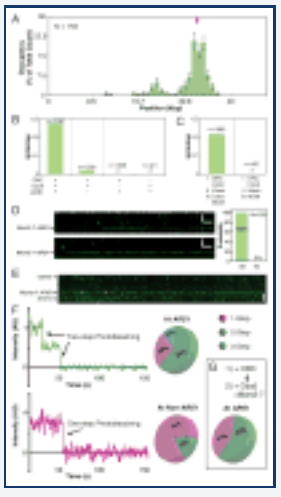
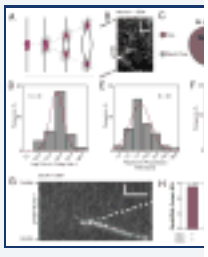

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