DNA Replication Pre-Initiation

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 79

This document contains 3 pathways (see Table of Contents)
Although, DNA replication occurs in the S phase of the cell cycle, the formation of the DNA replication pre-initiation complex begins during G1 phase.

**Editions**

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**DNA Replication Pre-Initiation**

**Stable identifier:** R-HSA-69002

**Compartments:** nucleoplasm, cytosol
DNA replication pre-initiation in eukaryotic cells begins with the formation of the pre-replicative complex (pre-RC) during the late M phase and continues in the G1 phase of the mitotic cell cycle, a process also called DNA replication origin licensing. The association of initiation proteins (ORC, Cdc6, Cdt1, Mcm2-7) with the origin of replication in both *S. cerevisiae* and humans has been demonstrated by chromatin immunoprecipitation experiments. In *S. cerevisiae*, pre-replicative complexes are assembled from late M to G1. In mammalian cells as well, pre-replicative complexes are assembled from late M to G1, as shown by biochemical fractionation and immunostaining. There are significant sequence similarities among some of the proteins in the pre-replicative complex. The ORC subunits Orc1, Orc4 and Orc5 are homologous to one another and to Cdc6. The six subunits of the Mcm2-7 complex are homologous to one another. In addition, Orc1, Orc4, Orc5, Cdc6, and the Mcm2-7 subunits, are members of the AAA+ superfamily of ATPases. Since the initial identification of these pre-RC components other factors that participate in this complex have been found, including Cdt1 in human, *Xenopus*, *S. pombe*, and *S. cerevisiae* cells.

**Literature references**


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In *S. cerevisiae*, two ORC subunits, Orc1 and Orc5, both bind ATP, and Orc1 in addition has ATPase activity. Both ATP binding and ATP hydrolysis appear to be essential functions in vivo. ATP binding by Orc1 is unaffected by the association of ORC with origin DNA (ARS) sequences, but ATP hydrolysis is ARS-dependent, being suppressed by associated double-stranded DNA and stimulated by associated single-stranded DNA. These data are consistent with the hypothesis that ORC functions as an ATPase switch, hydrolyzing bound ATP and changing state as DNA unwinds at the origin immediately before replication. It is attractive to speculate that ORC likewise functions as a switch as human pre-replicative complexes are activated, but human Orc proteins are not well enough characterized to allow the model to be critically tested. mRNAs encoding human orthologs of all six Orc proteins have been cloned, and ATP-binding amino acid sequence motifs have been identified in Orc1, Orc4, and Orc5. Interactions among proteins expressed from the cloned genes have been characterized, but the ATP-binding and hydrolyzing properties of these proteins and complexes of them have not been determined.

**Literature references**


Lane, WS., Tully, T., Hou, ZH., Jones, CJ., Velinzon, K., Quintana, DG. et al. (1999). latheo encodes a subunit of the origin recognition complex and disrupts neuronal proliferation and adult olfactory memory when mutant. Neuron, 23, 45-54.

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