Assembly of the ORC complex at the origin of replication

Davey, MJ., Kusic-Tisma, J., O'Donnell, M., Orlic-Milacic, M.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

03/03/2022
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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 79

This document contains 1 pathway and 11 reactions (see Table of Contents)
Assembly of the ORC complex at the origin of replication

Stable identifier: R-HSA-68616

Compartments: nucleoplasm

Human ORC1 can associate with DNA origin of replication sites independently of other origin of replication complex (ORC) subunits (Hoshina et al. 2013; Eladl et al. 2021). ORC1 localizes to condensed chromosomes during early mitosis (M phase) and serves as a nucleating center for the assembly of the ORC and, subsequently, the pre-replication complex. ORC1 remains associated with late replication origins throughout late G1. Upon S phase entry, ORC1 undergoes ubiquitin-mediated degradation, leading to dissociation of the ORC from chromatin (Kara et al. 2015).

Most human replication origins contain guanine (G)-rich sequences which may form G-quadruplex (G4) structures (Besnard et al. 2012) and these G4 structures may mediate the recognition of replication origins by ORC1 (Hoshina et al. 2013; Eladl et al. 2021). Besides binding to nucleosome-free replication origin DNA, ORC1 interacts with neighboring nucleosomes (Hizume et al. 2013), in particular with nucleosomes containing histone H4 dimethylated at lysine 21 (H4K20me2 mark), which is enriched at replication origins. Binding of ORC1 to H4K20me2 facilitates ORC1 binding to replication origins and ORC chromatin loading (Kuo et al. 2012, Zhang et al. 2015).

ORC1 binding sites are universally associated with transcription start sites (TSSs) of coding and non-coding RNAs. Replication origins associated with moderate to high transcription level TSSs (belonging to coding RNAs) fire in early S phase, while those associated with low transcription level TSSs (belonging to non-coding RNAs) fire throughout the S phase (Dellino et al. 2013).

ORC2 forms a heterodimer with ORC3, which is a prerequisite for the association of ORC5 and, subsequently, ORC4 (Ranjan and Gossen 2006; Siddiqui and Stillman 2007). ORC1 binds to the ORC(2-5) complex in the nucleus to form a stable ORC(1-5) complex (Radichev et al. 2006; Ghosh et al. 2011). ORC1 is necessary for the association of the ORC(2-5) complex to chromatin (Radichev et al. 2006). The ORC(2-5) complex exhibits a tightly autoinhibited conformation, with the winged-helix domain (WHD) of ORC2 completely blocking the central DNA-binding channel. Binding of ORC1 remolds the WHD of ORC2,
moving it away from the central channel and partially relieving the autoinhibition (Cheng et al. 2020, Jaremko et al. 2020). ORC6 associates with the ORC(1-5) complex to form the ORC(1-6) complex (Ghosh et al. 2011). The association of ORC6 with the ORC(1-5) complex is weak and it frequently does not co-immunoprecipitate with the other ORC(1-5) subunits. ORC4 is the only ORC(1-5) subunit that was shown to directly bind to ORC6 (Radichev et al. 2006). Some ORC6 mutations reported in Meier-Gorlin syndrome were shown to interfere with ORC6 incorporation into the ORC (Balasov et al. 2015).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Authorship</th>
<th>Editions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-06-05</td>
<td>Authored</td>
<td>Davey, MJ., O'Donnell, M.</td>
</tr>
<tr>
<td>2021-07-30</td>
<td>Authored, Revised</td>
<td>Kusic-Tisma, J.</td>
</tr>
<tr>
<td>2021-08-16</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
**ORC6 binds KPNA1 or KPNA6**

**Location:** Assembly of the ORC complex at the origin of replication

**Stable identifier:** R-HSA-9734670