# Molecular basis of DNA replication origin recognition in yeast

Supported by a National Natural Science Foundation of China (NSFC)/Research Grants Council of Hong Kong (RGC) Joint Research Scheme, a collaborative research team led by Gao Ning (高宁) (State Key Laboratory of Membrane Biology, School of Life Sciences, Peking University) and Bik-Kwoon Tye (Division of Life Science, Hong Kong University of Science and Technology) recently reported the cryo-EM structure of origin recognition complex (ORC) bound to DNA replication origin at a 3-Å resolution in *Nature* (2018, 559: 217—222). This high-resolution structure reveals how the *Saccharomyces cerevisiae* ORC is able to select the corrected sites for DNA replication to begin.

In eukaryotes, initiation of DNA replication can occur once and only once per cell cycle at each replication origin during S phase, to ensure a faithful inheritance of the entire genome by two daughter cells. Aberrant under- or over-duplication often induces genome instability, a hallmark of many cancers. ORC, a complex composed of six subunits, Orc1 to Orc6, is used to mark the sites for replication initiation in all eukaryotes. The dysfunction of ORC may lead to severe development disorders, such as Meier-Gorlin syndrome (MGS). MGS is a rare autosomal recessive hereditary dwarfism disorder, characterized by an intrauterine growth retardation and a postnatal slow-growth rate. Interestingly, most mutations associated with MGS were found in ORC1, ORC4, ORC6, CDT1, and CDC6, all of which are involved in replication initiation. However, patients with mutations in ORC1 and ORC4 appear to have the most severe short stature.

Although the function of ORC in replication initiation has been extensively studied during the past decades, the detailed molecular mechanisms of how ORC promotes origin selection and helicase loading are still poorly understood. In particular, despite the structures of ORC are highly conserved among eukaryotes, the specificity of ORC in DNA binding is highly diverged from yeast to human. It is known that specific DNA sequence plays a predominant role in certain yeasts while chromatin structure plays a predominant role in humans. To understand the mechanism underlying this divergence, it is crucial to obtain the high-resolution structures of ORC bound to origin DNA.

The cryo-EM structure determined in this study is a *Saccharomyces cerevisiae* ORC bound to a 72-bp ARS305 origin DNA containing both ARS consensus sequence (ACS) and B1 element. In this structure, the ORC encircles DNA through extensive interactions with both phosphate backbone and bases, and bends DNA at the ACS and B1 sites. In ACS region, the conserved thymine residues are specifically recognized by a conserved basic amino acid motif of Orc1 (Orc1-BP) inserting deeply into the minor groove, and by a species-specific helical insertion motif of Orc4 (Orc4-IH) inserting into the major groove. Similarly, in B1 element, basic patch motifs from Orc2 and Orc5 also insert into major and minor grooves to contact bases and to bend DNA. This study not only provides a structural framework for understanding how ORC recognizes and binds yeast origin DNA, also provides insight into the helicase loading mechanism in metazoans.

More importantly, understanding the atomic structure of the DNA replication machine (or any bio-molecular machines) is fundamentally important because all applied technology and engineering are founded in basic science/knowledge. The three-dimensional view of the DNA replication machines at atomic resolution may help us identify better targets for cancer therapy such that synthetic chemicals can be custom made to fit the target.

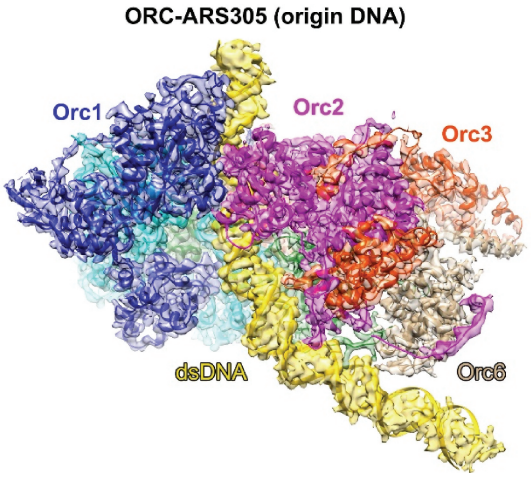


**Figure** Cryo-EM structure of *Saccharomyces cerevisiae* ORC bound to an origin DNA.