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Turning the replisome around

Helicases are ubiquitous molecular motors. By unwinding nucleic acids, they drive DNA replication, repair, transcription and recombination. In eukaryotes, the CDC45–MCM–GINS (CMG) helicase stands at the heart of the replisome, the machine that duplicates chromosomes. The replisome must coordinate DNA unwinding with DNA synthesis, which is asymmetric; it also handles nucleosome reassembly at the newly-replicated DNA and ensures faithful transmission of epigenetic information. Understanding the architecture and orientation of replisome components at the replication fork is therefore fundamental.

Georgescu and colleagues in the O'Donnell laboratory were the first to resolve the orientation of the CMG helicase at the fork. Using cryo-electron microscopy, they showed that DNA enters the CMG at the N-terminal of MCM hexameric ring and exits at the C-terminal. This orientation places the N-terminal of the MCM in front of the replication fork, and the C-terminal, comprising the ATPase motors, behind it — the opposite of what was long thought.

This finding was not just a structural detail, but a major conceptual shift in our understanding of DNA replication. By mapping the positions of key replisome components at the fork, the study set the stage for subsequent discoveries showing how DNA replication is orchestrated. The revised architecture places DNA polymerase α , which is responsible for priming of the lagging strand, in front of the fork and the leading-strand DNA polymerase ϵ behind it, suggesting tighter coordination between DNA unwinding and lagging-strand priming, while reducing the exposure of single-stranded DNA.

The new model also redefined ‘firing’ at origins of DNA replication: the two MCM rings, loaded head-to-head on the DNA at the origin, with their ATPase motors facing outwards, were thought to simply unzip DNA by moving apart. Instead, the MCM rings first embrace the opposite strands of DNA and bypass one another, thereby melting the DNA and providing an elegant built-in checkpoint to ensure both replisomes are ready.

Finally, this configuration places histone-binding motifs of the replisome ahead of the fork, thereby facilitating histone transfer to the newly-replicated DNA and faithful propagation of chromatin states. This unexpected twist in replisome architecture underscores the tight coordination of DNA unwinding, synthesis and chromatin maintenance.

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