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Mcm10: The glue at replication forks

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Minichromosome maintenance protein 10 (Mcm10) forms a DNA scaffold that coordinates the actions of multiple DNA replication factors. How Mcm10 accomplishes this task has proven to be a hard nut to crack. Indeed, even though it was discovered over 30 y ago, Mcm10 remains one of the more mysterious players in DNA replication and the cause of much controversy.[1] Most everyone in the replication field, however, is on board with some basic notions concerning Mcm10: first, that it is crucial to maintain genome integrity. Second, that Mcm10 is essential for the initiation of DNA replication. Putting those 2 pieces together, it is commonly believed that Mcm10's primary role in genome maintenance is its essential function as replication activator. A new study by Chadha and co-workers turns these beliefs upside down.[2] First shown to be required for DNA unwinding in *Xenopus laevis* egg extract,[3] Mcm10 is thought to activate the replicative helicase, composed of a Mcm2-7 core and 2 co-activators, cell division cycle protein 45 (Cdc45) and the go-ichi-ni-san (GINS) complex. The Cdc45:Mcm2-7:GINS (CMG) helicase is initially loaded onto DNA as an inactive dimer, and recent evidence suggested that Mcm10 facilitated the conversion into 2 active monomers.[1] Exactly how this might occur is still a matter of ongoing investigation, but the C-terminus of Mcm10 appears to be critical for this function, at least in budding yeast.[4]

Viewed in the light of this information, it is fair to say that the report by Chadha et al. comes as a big surprise. The authors convincingly show that depletion of Mcm10 from *Xenopus* egg extracts impedes DNA replication, but not – as one would have predicted – at the initiation step, but rather during elongation. A similar, albeit not identical, experimental system had yielded different results, clearly implicating Mcm10 in DNA unwinding, the first step in origin activation.[3] Although Chadha et al. can not formally exclude that substoichiometric amounts of Mcm10 that are barely detectable by western blot are sufficient to initiate replication in Mcm10-depleted extracts, their data are most compatible with a role for Mcm10 during DNA elongation. The key experiment implicating Mcm10 in this process utilizes a clever design in which replication can initiate, but elongation is impeded until the replicating chromatin is transferred into a second extract that allows for elongation, but prevents new origin firing.[2] In essence, this approach evaluates the ability of stalled replication forks to "restart." The kinetics of radiolabeled nucleotide incorporation in the present study are consistent with the notion that fork processivity is compromised in the absence of Mcm10 after forks have resumed activity. This data is also in agreement with a report that demonstrated reduced replication fork velocity upon Mcm10 depletion in human cells.[5]

Whether Mcm10 is an active replisome component and what its role may be has been a subject of debate.[1] In budding yeast, Mcm10 travels with the replication fork and interacts with factors that are enriched at lagging strands, such as DNA polymerase-α (pol-α), the replication clamp proliferating cell nuclear antigen (PCNA), and the 9-1-1 checkpoint clamp.[1] The observation that Mcm10:PCNA binding is essential in budding yeast is highly suggestive of a critical function during DNA elongation.[6] Chadha et al. significantly extend this concept by demonstrating that Mcm10 is the glue that keeps pol-α, PCNA, Cdc45 and specific GINS components on chromatin.[2]

Intriguingly, retention of some of these factors depends on the phosphorylation of Mcm10 at serine 630 (S630) by cyclin dependent kinase (CDK). Chromatin binding of Mcm10 is a prerequisite for phosphorylation. However, the reverse is not true, as DNA binding by Mcm10 occurs independently of S630 phosphorylation, although CDK activity is required.[2] S630 is conserved in mice and humans and failure to phosphorylate this residue results in enhanced sensitivity to the topoisomerase I inhibitor camptothecin. A similar scenario has been described for *mcm10* mutants in budding yeast,[7] however, the CDK-dependent modification of *Xenopus* Mcm10 reveals a novel regulatory step acquired during evolution.

Taken together, the authors provide compelling evidence for a model in which Mcm10 defies replication stress by actively stabilizing compromised replication forks, likely by preserving connectivity between the DNA unwinding and DNA polymerization entities.

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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