

Clearing jams in copy machinery

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Bacteria and humans use a number of tools to direct perhaps the most important function in cells -- the accurate copying of DNA during cell division. New research published this week in *Molecular Cell* from the laboratory of Rockefeller University's Michael O'Donnell, a Howard Hughes Medical Institute Investigator, now shows that one of these proteins, the beta sliding clamp, serves as a toolbelt from which the correct proteins are retrieved to enable DNA replication in the face of DNA damage.

The replication machinery inside the cell's nucleus is made up of a collection of enzymes including DNA polymerases, sliding clamps and clamp loaders. Bacteria have five known DNA polymerases (higher organisms such as humans have more). As the ring-shaped beta sliding clamp works its way along the DNA double helix, a network of proteins work together to unwind the two strands. Polymerases then add, in assembly line fashion, nucleotide bases -- the building blocks that make up DNA -- to convert the now-single-stranded templates into two new duplex DNA molecules.

The new research shows that two different DNA polymerases, the high fidelity Pol III replicase and the low fidelity Pol IV, coordinate their action to cross obstacles encountered in the replication process. They attach themselves at the same time to one beta sliding clamp. Pol III copies the original DNA, and acts as a proofreader to catch any misspellings and cuts any base that is wrong. But Pol III is a perfectionist, and can stall if it encounters a problem. Pol IV, on the other hand, lays down bases without checking for errors, keeping the

process moving even when Pol III gets stuck. The findings by O'Donnell and his colleagues show that, because both polymerases are bound simultaneously to the beta clamp, it can pull either of the polymerases out if its toolbelt as needed.

O'Donnell and his colleagues propose two explanations for how the polymerase switch is controlled.

"One possibility is that the beta clamp may sense when Pol III stalls, triggering a change in beta that pulls the polymerase from the primed site, allowing Pol IV to take over synthesis," O'Donnell says. Or, Pol III, upon stalling, may loosen its grip on the template and allow Pol IV to bind the primed site instead.

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