Structural features of high-fidelity DNA replication

Meindert H. Lamers
Dept. of Cell and Chemical Biology
Leiden University Medical Center
Einthovenweg 20
2333 ZC Leiden
M.H.Lamers@lumc.nl

During DNA replication, the DNA polymerase rapidly responds to different challenges in the DNA. Incorporation of a wrong nucleotide induces transfer of the DNA to the exonuclease where the misincorporated nucleotide is excised. Encounter with a damaged base in the template strand results in exchange with specialized repair DNA polymerases that can bypass the damaged base. Finally, on the lagging strand where DNA synthesis is discontinuous, the polymerase needs to repeatedly dissociate from the DNA, more than 10,000 times per replication cycle. How a single DNA polymerase is able to respond to all these different signals is not understood. Using cryo-electron microscopy and single molecule light microscopy, we reveal how the DNA polymerase responds to the different signals. Multiple cryo-EM structures show the molecular motions within the polymerase that enable it to adapt to the different signals, while the single molecule studies reveal a carefully orchestrated cooperation between different proteins that load and release the polymerase from the DNA.