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Structural insights on homologous recombination

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Homologous recombination (HR) is an essential biological process common to all living cells that maintains the genome integrity by faithfully repairing double-strand breaks (DSBs). The HR process searches the genome for a region that is homologous to the broken DNA and uses this region as a template to restore the DNA integrity, via the capture of the complementary strand that gets paired with the damaged DNA. Nucleofilaments resulting from the polymerization of a recombinase (RecA in prokaryotes) on each damaged DNA strand recruit the genomic DNA, test it for homology and promote strand exchange. The coordination of dynamic stages with different time and length scales enables the process to be simultaneously fast and stringent. By combining docking explorations and molecular dynamics simulations at the atomic level, we have integrated the results from 30 years studies into new structural insights on the HR process. We propose a mechanism for the initial recognition/strand exchange phase, where more than 80% of non-homologous sequences are eliminated, that uses mechanical tension in the DNA to locally destabilize the base pairing interactions in the searched DNA and perform swift homology tests via pairing exchange. We also investigated the role of ATP hydrolysis in the slower phases of HR using molecular dynamics simulations. These simulations, based on the hypothesis that the filament can change the internal arrangement of its monomers upon ATP hydrolysis, revealed how hydrolysis may promote reverse strand exchange in the filament. This provides a structural interpretation to the observed destabilization of the strand exchange product within filaments where ATP is hydrolyzed.

Biography

Chantal Prévost is a Researcher at the Theoretical Biochemistry Laboratory (LBT) of the French National Research Center (CNRS), in Paris. She has developed a strong expertise in studying complex biological processes *in silico* via the integrative exploration of unstable macromolecular self-assembly substates. She has elaborated new algorithms for flexible macromolecular docking and protein fiber modeling. She presently applies this expertise to tackling the mechanism of homologous recombination as well as exploring the architecture of oligomeric assemblies, in collaboration with the Prentiss team in Harvard University, USA.

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