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Integrative approaches to study the structure and motions of DNA sliding clamps

Alfredo De Biasio
Elettra-Sincrotrone Trieste, Italy

Sliding clamps encircle DNA and tether polymerases and other proteins to the genomic template, and are essential factors in DNA replication. Because of the transient interaction that the clamps establish with DNA, the clamp-DNA interface eluded a thorough structural characterization, so that the molecular mechanism for clamp sliding on DNA remained obscure. Here, I will show how the combined use of high-resolution techniques (X-ray crystallography and NMR) and molecular dynamics (MD) simulations allowed to visualize the interactions between the Proliferating Cell Nuclear Antigen (PCNA) – the eukaryotic sliding clamp – and DNA, and to decipher the mechanics of sliding. In addition, recent findings show that the DNA sliding surface of PCNA can be modified to regulate the resistance to DNA damage. From a structural viewpoint, I will reflect on these findings which open a new perspective on PCNA function and offer opportunities to develop tools to manipulate the DNA damage response in cancer treatment.

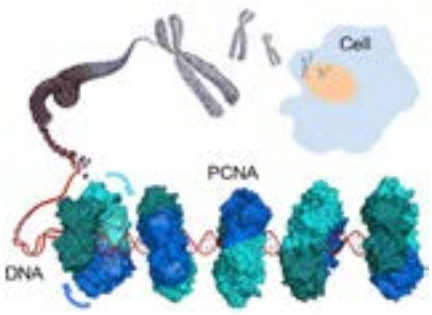

Figure1: *PCNA is a ring-shaped trimeric protein that encircles DNA and binds the polymerases during DNA replication and repair. The integrative use of structural and computational methods allowed to describe the sliding mechanism of PCNA, a spiral motion that keeps the orientation of PCNA relative to DNA invariant.*

Biography

Alfredo De Biasio has work focus on the structure and function of DNA sliding clamps and their complexes operating in DNA replication and repair. He is particularly interested in understanding the mechanisms of sliding of the eukaryotic clamp PCNA, and how these mechanisms are modulated by modifications of the PCNA sliding surface, and the implications in DNA damage avoidance. These problems are tackled by an integrative approach that combines X-ray crystallography, NMR and MD simulations.

alfredo.debiasio@elettra.eu

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