Laboratoire d biosciences
Ecole Polytechnique CNRS INSERM IP Paris

Jeudi 23 Janvier 2020 à 11h
Ecole Polytechnique
Amphithéâtre Grégory

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Advances in understanding Topoisomerase I molecular mechanisms

Torsional tension in DNA is both an important factor for the initiation of transcription and replication, and the direct consequence of strands separation during the same cellular processes. In eukaryotes, Topoisomerase I (Top1) removes torsional stresses associated with DNA replication and transcription and has essential functions in gene expression regulation. While Top1 has major cellular functions, the enzyme can also have deleterious effects. Indeed, Top1 activity involves transient DNA breaks that can be stabilized spontaneously (1), or by specific drugs such as camptothecin, the toxicity of Top1-induced breaks being used in cancer treatments (2).
The current structural data suggests that Top1 molecular mechanism should involve two major states. The DNA molecule should enter Top1 cavity while the enzyme is in an open state and DNA cleavage, relaxation and religation should occur while Top1 is in a closed state (3). Despite active research on Top1, the enzyme has been structurally characterized only in its closed state (4, 5). I investigated Top1 structure using an enzyme from one hyperthermophilic archaeon, *Caldiarchaeum subterraneum* that is both highly similar to the eukaryotic enzyme, and highly thermostable (6). This enzyme allowed me to solve the first structure of Top1 in an open conformation. This novel structure reveals that Top1 is a bimodular enzyme, in which one DNA binding module, and one regulatory module are linked with one flexible hinge loop, which allows the opening/closing of the enzyme. This Top1 structure brings new insight regarding the dynamic of the enzyme, and raises questions about the specificity of the enzyme towards specific DNA structures including supercoiled DNA and non-canonical DNA structures such as G-quadruplexes.

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