Snapshot: SMC Protein Complexes II

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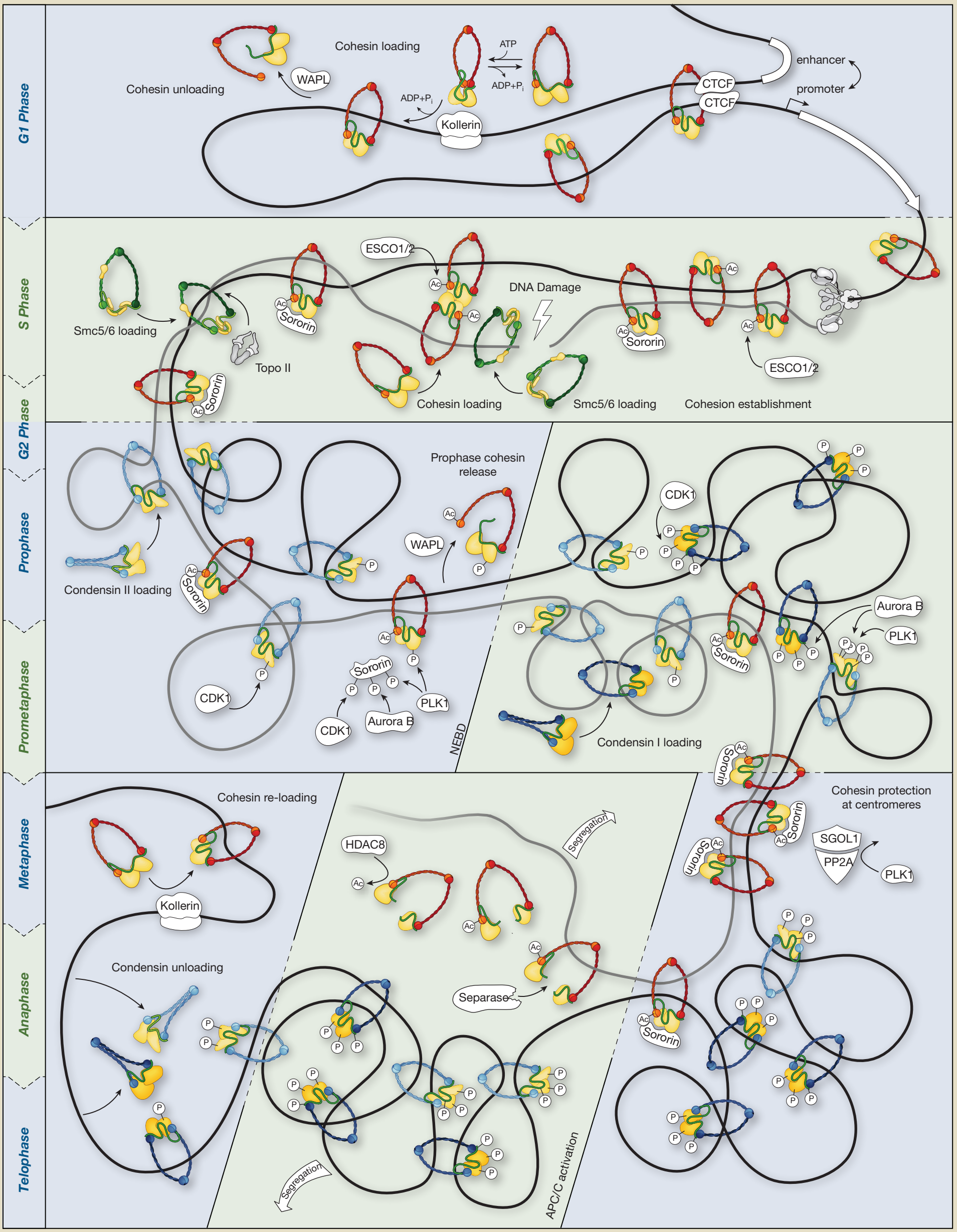

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This two-part SnapShot depicts the composition and architecture of SMC protein complexes and their regulators (in part I) and their roles at different stages of the cell cycle (in part II).

Part II: The chromosome replication/segregation cycle

Multi-subunit SMC complexes have manifold functions during chromosome segregation and genome maintenance in bacteria, archaea and eukaryotes. Generally, they form large annular structures that entrap DNA molecules to organize and compact chromosomal DNA.

Cohesin complexes are loaded onto chromosomes during most stages of the cell cycle with the help of the two-subunit Kollerin complex in a manner that depends on ATP hydrolysis by their SMC1–SMC3 subunits. Cohesin is unloaded by the WAPL protein, which presumably opens a DNA 'exit gate' between the SMC3 and kleisin subunits of the Cohesin ring. Cohesin can mediate the regulation of gene expression, possibly by the formation of DNA loops between enhancer and promoter elements, for example at binding sites of the CTCF protein.

During DNA replication, a fraction of Cohesin becomes stabilized on chromosomes via acetylation of its SMC3 subunit by the ESCO1 and ESCO2 acetyltransferases, which prevents opening of the DNA exit gate by WAPL. This fraction of Cohesin mediates sister chromatid cohesion during G2 phase and during most of mitosis. The Smc5/6 is loaded onto chromosomes during DNA replication at sites of DNA damage, such as inter-strand cross-links or DNA double strand breaks, and at sites of sister DNA intertwining. In several animal species, Sororin binds to Cohesin during G2 phase and protects it from the action of WAPL.

During prophase, a large fraction of Cohesin–Sororin complexes located at chromosome arms is phosphorylated by CDK1, Aurora B and PLK1 kinases and released from chromosomes in a WAPL-dependent manner. Concomitantly, nuclear Condensin II complexes become enriched on chromosomes and to initiate sister chromatid condensation (axial shortening) and resolution. Following nuclear envelope breakdown (NEBD) at the onset of prometaphase, Condensin I gains access to chromosomes and contributes to the lateral compaction of chromatids. Both Condensin complexes are activated by phosphorylation by CDK1, Aurora B kinase and PLK1.

Cohesin remains protected from the action of WAPL near centromeres by its dephosphorylation by Shugoshin–PP2A complexes. At the onset of anaphase, the Cohesin complexes that remained bound to chromosomes are proteolytically cleaved by Separase to finally trigger the segregation of the condensed sister chromatids towards opposite poles of the cell by the mitotic spindle. Unloading of Condensin during telophase is thought to result in the decondensation of chromatids. At the same time, Cohesin complexes start to be re-loaded onto chromosomes following the deactylation of their SMC3 subunits by HDAC8.

ABBREVIATIONS

APC/C, Anaphase Promoting Complex/Cyclosome; CDK1, Cyclin-Dependent Kinase 1; NEBD, Nuclear Envelope Breakdown; PLK1, Polo-Like Kinase 1

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