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Cooperative Binding and the Control of DNA Replication Timing in Bacteria

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Bacteria have evolved a sophisticated strategy to coordinate DNA replication with cell growth, enabling them to grow rapidly in nutrient-rich conditions even when the cell doubling time is shorter than the duration of a single round of replication. However, the precise mechanism by which the replication program is coupled to the cell cycle remains debated.

Most bacteria have a circular chromosome with a single origin of replication, where the DNA double helix is unwound and replication begins. Initiation is triggered by the protein DnaA, whose accumulation in an active, initiation-competent state is tightly regulated. Two major processes control this regulation: the titration at chromosomal binding sites, and the cycling between the active and inactive forms of DnaA.

DnaA binds to high-affinity sites distributed along the chromosome, effectively reducing the concentration of free, unbound DnaA. Although DnaA is continuously produced such that its total concentration remains approximately constant throughout the cell cycle, when replication is not occurring, the concentration of chromosomal binding sites decreases due to volume expansion. As these titration sites become saturated, the accumulated free DnaA increasingly binds to sites at the origin to trigger initiation. During replication, new binding sites are created as the DNA strands are copied, which in turn reduce the free DnaA concentration, making premature re-initiation unlikely.

However, this feedback alone is not sufficient to ensure robust control of initiation timing. An additional layer of regulation is provided by the ATP-dependent inactivation of DnaA following initiation.

While replication initiation is inherently stochastic, bacterial cells nonetheless achieve remarkably accurate timing and maintain synchrony of origin firing across multiple replication forks. We present a statistical model based on cooperative binding of DnaA at the origin to explain how bacterial cells achieve such precise replication timing despite the intrinsic stochasticity of the underlying molecular processes

Authors: SASSI, Alberto Stefano (Okinawa Institute for Science and Technology); Prof. PIGOLOTTI, Simone (Okinawa Institute for Science and Technology)

Presenter: SASSI, Alberto Stefano (Okinawa Institute for Science and Technology)