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Excluded stand control of hexameric helicase DNA unwinding

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Hexameric DNA helicases are a nexus of control for both the initiation and elongation phases of DNA replication. These toroidal enzymes encircle and translocate preferentially on one strand with specific polarities dependent on their families and organismal domains. Over the past few years, there has been an increasing amount of evidence to suggest that the excluded-strand plays a significant role during unwinding by interacting with the helicase's outer surface in a Steric Exclusion and Wrapping (SEW) mode. This excluded strand interaction appears to be dynamic and can differentially regulate the speed of DNA unwinding in diverse organisms. We have investigated the interaction of the excluded strand with the outer surface of the bacterial, archaeal, and human hexameric helicases using a variety of biochemical, biophysical, and genetic techniques. We have not only confirmed this external interaction with the exterior surface, we can also show that this interaction regulates the DNA unwinding rate dependent on the unwinding polarity of the organism. Interaction of the lagging strand on the exterior of the archaeal homohexameric SsoMCM helicase is required for efficient and productive unwinding. We have mapped the binding orientation of the homohexameric SsoMCM onto model DNA fork substrates using site-specific cleavage agents to show an intermediate in the DNA loading process. Alternatively, the interaction of the leading strand on the exterior of the bacterial DnaB helicase reduces unwinding consistent with the leading strand polymerase being intricately coupled with DnaB during normal replication conditions. *In vivo*, genetically edited exterior mutations of DnaB have growth defects and sensitivities to DNA damage agents. Therefore, interactions with the excluded DNA strand has a previously unknown but influential role in controlling the speed of the replisome, the efficiency of DNA unwinding, and maintaining genomic integrity.

Biography

Michael Trakselis has expertise in a number of overlapping disciplines of molecular biology, biochemical and biophysical analysis of enzymes, molecular genetics, and cell biology. His laboratory examines the molecular mechanisms and pathways of DNA helicases and polymerases involved in replication and repair. The goals are to uncover novel contacts and interactions that advance our fundamental understanding of these complex processes as well as provide novel targets for inhibition.

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