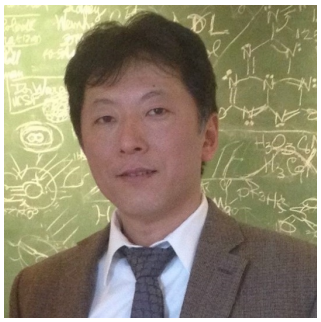

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Biography

Katsuhiko Murakami started his research career as a graduate student working under Prof. Akira Ishihama in the National Institute of Genetics and the Graduate University of Advanced Studies in Japan. His thesis title is "Functional analysis of the carboxyl-terminal transcription regulation domain of Escherichia coli RNA polymerase α subunit" and he received Ph. D. in 1997. He engaged in postdoctoral study at the Rockefeller University (1998-2003) for determining the X-ray crystal structure of bacterial RNA polymerase. He joined the Department of Biochemistry and Molecular Biology at Pennsylvania State University as an Assistant Professor in 2003 and became a full Professor in 2015.

Abstract

"Structural basis of bacterial RNA polymerase transcription initiation and inhibition by anti-tuberculosis drug rifamycin"

The bacterial RNA polymerase (RNAP) holoenzyme containing catalytic core enzyme and promoter binding σ factor initiates RNA synthesis by de novo RNA priming. We determined the structure of de novo transcription initiation complex that reveals unique contacts of the initiating ribonucleotides (iNTPs) with the template DNA and RNAP and demonstrate the importance of these contacts for de novo transcription initiation (1). Using this bacterial RNAP and promoter DNA complex crystal, we have established a method, time-dependent soak-trigger-freeze X-ray crystallography, to monitor the RNA synthesis reaction inside of crystals in real-time. We revealed that after RNA synthesis, pyrophosphate (PPi), a byproduct of the reaction, remains bound at the active site of RNAP to prevent mis-incorporation. Rapid release of PPi from the active site occurs only correct NTP coming to the active site.

Reiterative transcription is a noncanonical form of RNA synthesis in which a nucleotide specified by a single base in the DNA template is repetitively added to the nascent transcript. We determined a series of structures at early stage of reiterative RNA synthesis and revealed a mechanism of RNA slippage during the reiterative transcription (2).

The bacterial RNAP inhibitor rifamycin has been used as a first line and cornerstone of anti-tuberculosis (TB) treatment. However, increased occurrence of rifamycin-resistant TB containing RNAP mutations have become a growing problem worldwide. Over 40% of rifamycin-resistant TB mutants carry a single-type of RNAP point mutation, at RpoB-S531L. We determined the crystal structures of RNAP containing S531L and other clinically common resistant mutations RpoB-H526Y and RpoB-D516V. Our structural analysis revealed the unique mechanism by which the S531L mutation reduces rifampin binding to RNAP relative to the H526Y and D516V mutants (3). We also reported an analog of the rifamycin, kanglemycin A (KglA), that inhibits rifamycin-resistant RNAP and is effective against multidrug-resistant TB. Thus, KglA represents a key starting point for the development of a new class of rifamycin to fight against drug-resistant TB (4).

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