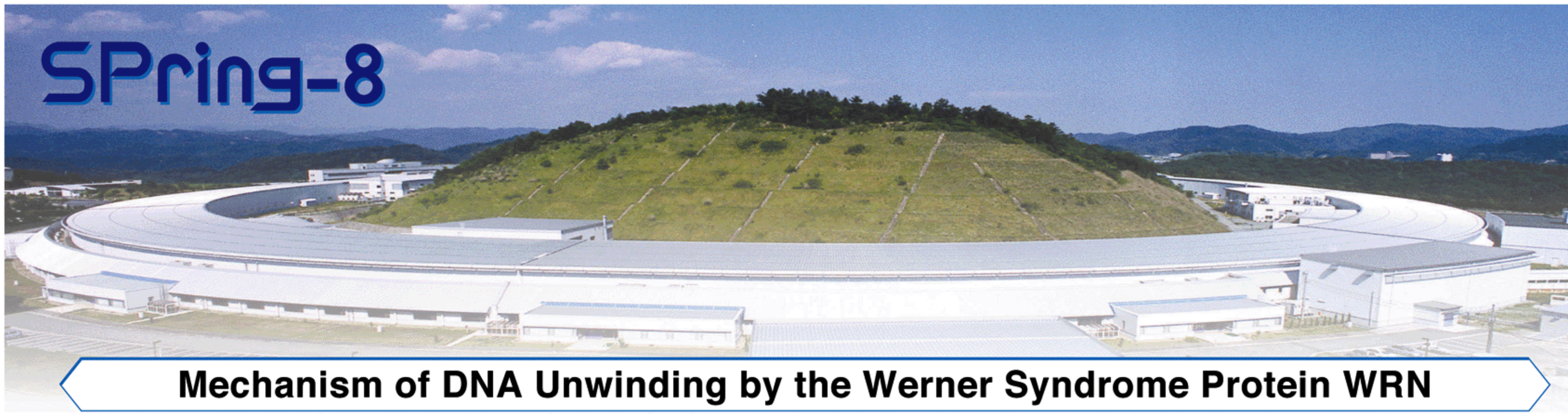

Mechanism of DNA Unwinding by the Werner Syndrome Protein WRN

Dr. Ken Kitano and coworkers from the Nara Institute of Science and Technology (NAIST) have used SPring-8 beamlines BL41XU (Structural Biology I) and BL44XU (Macromolecular Assemblies) to determine the first three-dimensional structure of the DNA-bound form of WRN (Werner syndrome helicase), a protein that protects humans from accelerated aging disorder.

In the cells, many aspects of nucleic-acid metabolism require that complementary strands of DNA be separated (unwound). The unwinding reactions are catalyzed by the enzymes called DNA helicases. A RecQ family of DNA helicase WRN has gained focus due to rare genetic disease called Werner syndrome, which arises from a mutation in the gene that encodes this protein. The Werner patients (most of them are of Japanese origin) begin rapidly aging in their teens. WRN is known to play a key role in protecting the genome against deleterious changes; however, the mechanism underlying the DNA binding and unwinding activities remained unclear.

The research team has determined an X-ray crystal structure of the WRN core fragment (RecQ-conserved domain) in complex with a DNA duplex (Figure 1) [1]. The structure successfully captured a DNA-unwinding event by the WRN, which gave the first-ever explanation for the specialized activities of the enzyme toward replication and recombination intermediates such as replication forks, Holliday junctions, and D-loops (Figure 2). It appears as if the protruding hairpin motif, which they named "DNA strand-separating knife," acts as a scalpel to unpair a Watson-Crick base pair from the duplex terminus.

Their results have greatly advanced our understanding of the functions of WRN as well as another RecQ member BLM (Bloom syndrome helicase; mutation in this protein causes a rare cancer predisposition disease called Bloom syndrome) in terms of the prevention of accelerated aging and cancer [1, 2].

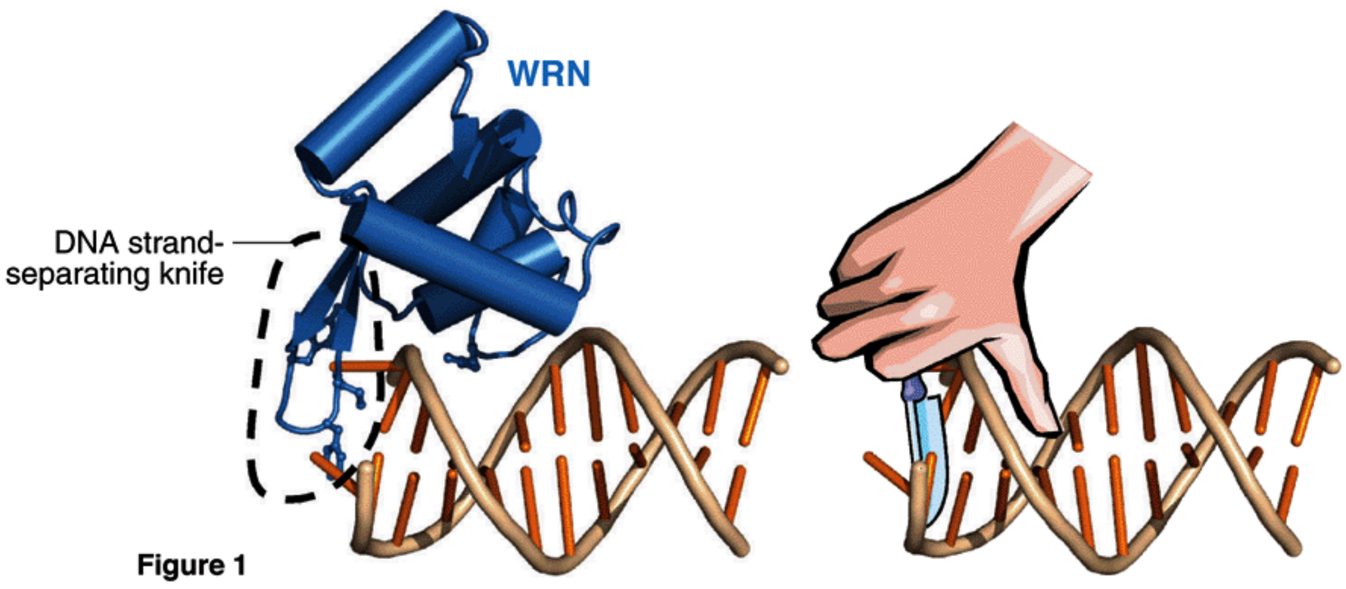

Figure 1

References:
[1] Kitano, K., Kim, SY., Hakoshima, T. (2010). *Structure*, **18** (2), 177-187.
[2] Kitano, K., Yoshihara, N., Hakoshima, T. (2007). *J. Biol. Chem.*, **282** (4), 2717-2728.

Figure 1
Structure of WRN RecQ-conserved domain bound to DNA. The structure shows that the domain melts one base pair at the duplex end upon binding. The protruding hairpin motif acts just like a knife to unwind DNA.

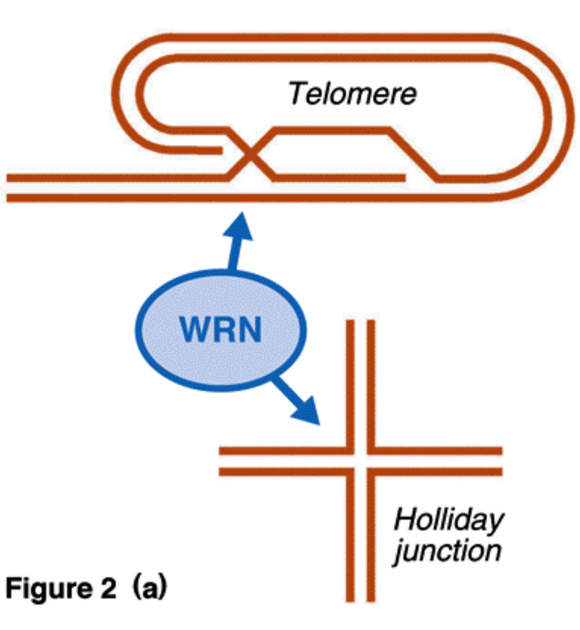

Figure 2 (a)

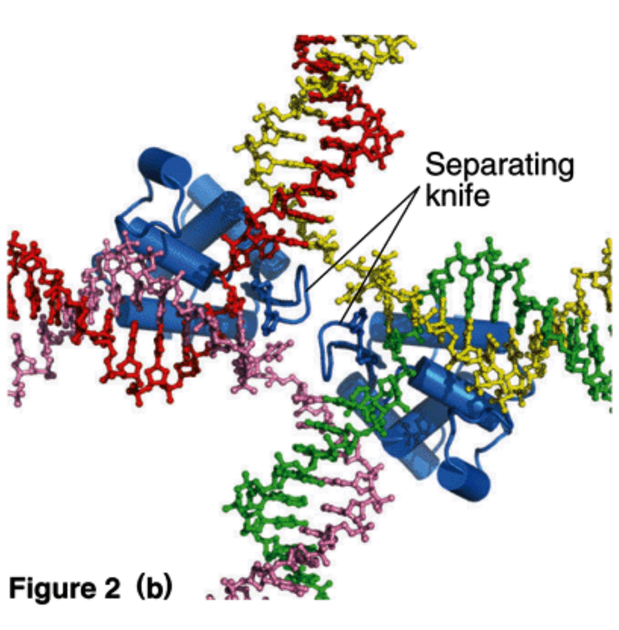

Figure 2 (b)

Figure 2
Resolutions of noncanonical DNA structures by WRN. **(a)** WRN is proposed to catalyze the resolution of telomeric D-loops and Holliday junctions. **(b)** Three-dimensional simulation model depicting the resolution of Holliday junction by WRN. The two RecQ-conserved domains of WRN are shown in blue. A small hole of the Holliday junction can accommodate one pair of separating knives without steric hindrance.

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