ABSTRACT

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DNA and Chromatin Dynamics: Discovery of a Novel ATP-dependent DNA Rewinding Motor

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The SNF2-like family of proteins comprises the ATPase subunits of all of the known chromatin remodeling factors as well as factors involved in transcription and DNA repair. We examined the function of human HARP, a distant member of the SNF2-like family. It was previously found that mutations in HARP are responsible for a rare disease termed Schimke immuno-osseous dysplasia (SIOD), but the molecular function of the protein was not known. We discovered that HARP possesses a new biochemical activity – it functions as an ATP-driven annealing/reverse helicase. Unlike a helicase that unwinds double-stranded DNA to yield single-stranded DNA bound by RPA (replication protein A, the major single-stranded DNA-binding protein in eukaryotes), HARP rewinds complementary, RPA-bound single-stranded DNA bubbles to give double-stranded DNA. Other related ATPases, including the DNA translocase Rad54, do not exhibit annealing/reverse helicase activity. Analysis of mutant HARP proteins suggested that SIOD is caused by a deficiency in annealing helicase activity. Moreover, the pleiotropy of HARP mutations is consistent with the function of HARP as an annealing helicase that acts throughout the genome to oppose the action of DNA-unwinding activities in the nucleus.