sites. The structure reveals a ternary complex in which protein homo-dimerization is mediated by the specific arrangement of the two Ets-1 binding sites and demonstrates how Ets-1 transcription factor dimerizes by forming a central protein/DNA interface that involves several residues from a loop connecting the N-terminal autoinhibitory region and the ETS domain. Ets-1 variants, in which residues involved in protein-protein interaction are mutated, lose the ability for DNA-mediated dimerization and stromelysin-1 promoter transactivation. The X-ray structure of the Ets-1/DNA/Ets-1 complex formed on the stromelysin-1 promoter shows for the first time how Ets-1 transcription factor can function as a homodimer contrary to previous structures where Ets-1 was bound to DNA as a monomer or formed complexes with other transcription factors on DNA. Thus, our data unravel the molecular basis of the ability of Ets-1 to function as a facultative dimeric transcription factor and play an important role in the transcription regulation of the stromelysin-1 promoter.

Keywords: Ets-1, transcription regulation, protein-DNA complexes

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Structure of the FOXO3a-DBD/DNA complex suggests the effects of post-translational modification

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FOXO3a is a transcription factor of the FOXO family. The FOXO proteins participate in multiple signaling pathways, and their transcriptional activity is regulated by several post-translational mechanisms, including phosphorylation, acetylation and ubiquitination. Because these post-translational modification sites are located within the C-terminal basic region of the FOXO DNA-binding domain (FOXO-DBD), it is possible that these post-translational modifications could alter the DNA-binding characteristics. To understand how FOXO mediate transcriptional activity, we report here the 2.7 Å crystal structure of the DNA-binding domain of FOXO3a (FOXO3a-DBD) bound to a 13-bp DNA duplex containing a FOXO consensus binding sequence (GTAAACA). Based on a unique structural feature in the C-terminal region and results from biochemical and mutational studies, our studies may explain how FOXO-DBD C-terminal phosphorylation by protein kinase B (PKB) or acetylation by cAMP-response element binding protein (CBP) can attenuate the DNA-binding activity and thereby reduce transcriptional activity of FOXO proteins. In addition, we demonstrate that the methyl groups of specific thymine bases within the consensus sequence are important for FOXO3a-DBD recognition of the consensus binding site.

Keywords: FOXO3a, winged/helix, DNA complex

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Structural basis for human mitochondrial DNA polymerase processivity

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Replication of mitochondrial DNA (mitoDNA) is an essential process for maintenance of the molecule which encodes a subset of components for oxidative phosphorylation. The replication is conducted by a nuclear-coded DNA polymerase gamma (Polg) which also has exonuclease activity as proofreading function and dRP lyase activity as repair function. Interestingly, mutations in Polg can cause an impaired mitoDNA replication, which are implicated in human mitochondrial diseases. In addition, human Polg is the target of adverse reactions of anti-HIV reagents and is in part responsible for drug toxicities. To illustrate the structural basis for mitoDNA replication and facilitate rational design of antiviral drugs, we determined crystal structure of human Polg holoenzyme to 3.2 Å resolution. The structure revealed heterotrimer architecture of the enzyme with a monomeric catalytic subunit (Polg A) and a dimeric accessory subunit (Polg B). The two subunits form extensive interaction thereby providing a novel mechanism for high processivity of DNA replication. Polg A folds into three distinct domains, a polymerase (pol) and a nuclease (exo) domains, as well as a spacer domain sandwiched between the above two domains. While the pol and exo domains present high homology with those of other members of DNA Pol I family, the spacer domain shows a unique fold where a large area of subunit interaction are formed. The structure of the spacer domain also provides an explanation for its ability to coordinate the enzymatic activities of pol and exo domains as well as increasing processivity of Polg A. The structural information of Polg would set the stage of further understanding the mechanism for mitoDNA replication as well as mitochondrial toxicity of anti-HIV drug.

Keywords: DNA polymerase gamma, processivity, mitochondria

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Crystal structure of the HRDC domain of human Werner syndrome protein, WRN

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Werner syndrome is a human premature aging disorder characterized by chromosomal instability. The disease is caused by the functional loss of WRN, a member of the RecQ-helicase family that plays an important role in DNA metabolic pathways. WRN contains four structurally folded domains comprising an exonuclease, a helicase, a winged-helix, and a helicase-and-ribonuclease D/C-terminal (HRDC) domain. In contrast to the accumulated knowledge pertaining to the biochemical functions of the three N-terminal domains, the function of C-terminal HRDC remains unknown. Recently we determined the crystal structure of the human WRN HRDC domain (Kitano et al. J. Biol. Chem. 2007; 282 2717-28). The domain forms a bundle of alpha-helices similar to those of Saccharomyces cerevisiae Sgs1 and Escherichia coli RecQ. Surprisingly, the extra ten residues at each