ZBTB24 regulates gene transcription by recognizing the core promoter of *CDCA7*

R. Ren[1], John R. Horton[1], Xing Zhang[1], Taiping Chen[1] and Xiaodong Cheng[1]

[1] Department of Epigenetics and & Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, Houston, TX 77030

Email Contact: rren1@mdanderson.org

Abstract

Immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome is a genetic disorder characterized by hypomethylation of (peri)centromeric satellite DNA. Four ICF-associated genes have been identified: *DNMT3B*, *ZBTB24*, *CDCA7*, and *HELLS* [1,2,3,4]. While the roles of DNMT3B (a DNA methyltransferase) and HELLS (a DNA helicase) in DNA methylation are well established [1,2,4], the functions of ZBTB24 and CDCA7 are largely unknown. ZBTB24, which contains eight tandem zinc fingers (ZFs), regulates gene transcription by binding a promoter sequence of *CDCA7* [5]. In this study, we determined the crystal structure of the C-terminus ZF domain of ZBTB24 (ZF4-8) in complex with an identified 19-base pair oligonucleotide containing consensus sequence. Our crystal structure reveals that ZF4 spans along the DNA phosphate backbone and the last four fingers (ZF5-8) interact with the major groove of 13-base pair motif. ZF6-8 follow the one-finger-three base rule, whereas ZF5 recognizes four bases. We also measured the dissociation constant (K_D) between this ZF domain and oligonucleotides. The binding data confirm the specificity of ZBTB24 where deletion of ZF4 does not affect specific DNA binding. Our structural data demonstrates that ZBTB24 directly activates CDCA7 transcription and provides important insights into how ZBTB24 recognizes its target DNA sequence.

References

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