RESEARCH ARTICLE

Mechanisms of OCT4-SOX2 motif readout on nucleosomes

Alicia K. Michael[1,*], Ralph S. Grand[1,*], Luke Isbel[1,*], Simone Cavadini[1], Zuzanna Kozicka[1,2], Georg Kempf[1], …
+ See all authors and affiliations

Science 26 Jun 2020:
Vol. 368, Issue 6498, pp. 1460-1465
DOI: 10.1126/science.abb0074

Engaging the nucleosome

Cell identity is defined by gene expression patterns that are established through the binding of specific transcription factors. However, nucleosomal units limit access of transcription factors to specific DNA motifs within the mammalian genome. To study how transcription factors bind such chromatinized, nucleosome-embedded motifs, Michael *et al.* focused on the pluripotency factors OCT4 and SOX2. They systematically quantified the relative affinities of these factors at different motif positions throughout the nucleosome, enabling structure determination of OCT4-SOX2–bound nucleosomes by cryo–electron microscopy. OCT4 and SOX2 bound cooperatively to strengthen DNA-binding affinity and resulted in DNA distortions that destabilized the nucleosome. This analysis reveals position-dependent binding modes that were validated in vivo, providing insights on how transcription factors read out chromatinized motifs.

Science, this issue p. **1460**

Abstract

Transcription factors (TFs) regulate gene expression through chromatin where nucleosomes restrict DNA access. To study how TFs bind nucleosome-occupied motifs, we focused on the reprogramming factors OCT4 and SOX2 in mouse embryonic stem cells. We determined TF engagement throughout a nucleosome at base-pair resolution in vitro, enabling structure determination by cryo–electron microscopy at two preferred positions. Depending on motif location, OCT4 and SOX2 differentially distort nucleosomal DNA. At one position, OCT4-SOX2 removes DNA from histone H2A and histone H3; however, at an inverted motif, the TFs only induce local DNA distortions. OCT4 uses one of its two DNA-binding domains to engage DNA in both structures, reading out a partial motif. These findings explain site-specific nucleosome engagement by the pluripotency factors OCT4 and SOX2, and they reveal how TFs distort nucleosomes to access chromatinized motifs.