

Stem cell transcription factors meet chromatin under the computational nanoscope

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I will present our efforts to understand how master regulators of stem cell pluripotency are recognizing genomic DNA in different contexts. Transcription factors such as Oct4 and Sox2 are essential proteins that bind DNA regulatory elements to establish gene regulation programs for the maintenance and induction of stem cell properties. They recognize DNA in different regions of the nuclear chromatin, the structure in which the genomic DNA is packed in the cell. Chromatin is a highly dynamic structure formed by packing of fundamental units, nucleosomes in arrays of different sizes and shapes. The nucleosome wraps 147 base pairs of DNA around a histone core formed by 4 histone proteins, each occurring twice. DNA recognition by transcription factors is highly dependent on the local chromatin structure. In nucleosome depleted regions, Oct4 and Sox2 recognize DNA mostly together via a cooperative heterodimerization mechanism. When nucleosomes are present, Oct4 and Sox2 recognize their binding sites on wrapped DNA and induce local opening of nucleosomes and chromatin. Because of this ability, they were classified as pioneer transcription factors. We now start to understand the mechanisms by which pioneer transcription factors unravel genomic DNA wrapped in nucleosomes. I will show how we are discovering key details of these mechanisms with the computational nanoscope, visualizing Oct4- and Sox2-nucleosome complexes by molecular modeling and molecular dynamics simulations. Besides contributing to expanding our knowledge about protein-DNA recognition in chromatin, our work may also inform future strategies to optimize cell fate transitions for therapeutic purposes.