Elucidating the molecular assembly of pioneering transcription factors with nucleosomes using cryo-EM

Michael, A.[1], Matsumoto, S.[1], Cavadini, S.[1] and Thomä, N.[1]

[1] Friedrich Miescher Institute for Biomedical Research, Switzerland

Specific regulation of genes is essential for cellular life. In mammals, transcription factors play a critical role in this process as they distinctly mark regions of the genome for expression. Although transcription factors recognize and bind to specific DNA motifs, their association with DNA and downstream regulation is also dependent on the chromatin environment. The presence of nucleosomes and epigenetic modifications along the genome, as well as the three-dimensional chromatin organization, can regulate transcription factor recruitment. Indeed, transcription factor binding to DNA is most often favored in nucleosome-free regions. However, a small number of 'pioneer' transcription factors, are able to access restricted, nucleosome-rich, regions of the genome and trigger subsequent gene activation. How a does a transcription factor recognize its specific sequence within condensed chromatin to regulate gene activation and accessibility? Numerous transcription factors essential for development have been found to bind silent chromatin; however, how they might specifically recognize their cognate DNA sequence in the context of a nucleosome is still unclear. Most transcription factors recognize specific 6 - 8 bp DNA sequences to regulate gene expression. Nucleosomal DNA is largely inaccessible to canonical sequence-specific recognition as it is wrapped around histones, only exposing partial DNA motifs. Yet, some pioneer transcription factors are able to overcome this apparent barrier and specifically bind DNA while it is simultaneously engaged with histones, how do they do so? Using single particle cryo electron microscopy (cryo-EM) we aim to determine the molecular details of the interaction between pioneer transcription factors and nucleosomes. In addition, we apply *in vitro* biochemistry, and cell biology to examine the molecular mechanisms that underlie recognition of specific-DNA motifs by diverse families of transcription factors in the context of the closed chromatin. We will present recent updates on our findings.

Funding: EMBO ALTF 352-2017