CDB SEMINAR

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16:00~17:00　C1F Auditorium

Induction of Pluripotency

Summary

Pluripotent stem cells are characterized by open chromatin and high transcription levels, which is achieved via auto-regulatory and feed-forward transcription factor loops. The reprogramming of mouse and human somatic cells into pluripotent stem cells, designated as induced pluripotent stem (iPS) cells, was first successfully achieved using fibroblasts as the starting population in 2006 by Kazutoshi Takahashi and Shinya Yamanaka. However, it remains unknown how this leads to the multitude of epigenetic changes observed during the reprogramming process. Interestingly, Oct4 is the only factor that cannot be replaced by other members of the same family to induce pluripotency. To understand the unique role of Oct4 in reprogramming, we determined the Structure of its POU domain bound to DNA(1).

We show that the linker between the two DNA-binding domains is structured as an α-helix and exposed to the protein’s surface, in contrast to the unstructured linker of Oct1. Point mutations in this α-helix alter or abolish the reprogramming activity of Oct4, but do not affect its other fundamental properties. Based on mass spectrometry studies of the interactome of wild-type and mutant Oct4, we propose that the linker functions as a protein-protein interaction interface and plays a crucial role during reprogramming by recruiting key epigenetic players to Oct4 target genes. Thus, we provide molecular insights to explain how Oct4 contributes to the reprogramming process.

Gene-specific factors for RNA polymerase II-mediated transcription of pluripotency genes recruit transcriptional co-factors and chromatin regulators in order to control access and activity of the basal transcription machinery. Here, we show that TFIID knockdown affected the pluripotent circuitry in ES cells and inhibited reprogramming of fibroblasts(2). TFIID with TAF4 and the pluripotency factors form a feed-forward loop to induce and maintain a stable transcription state. Strikingly, transient expression of TFIID subunits greatly enhanced reprogramming. These results show that TFIID is critical for transcription factor-mediated reprogramming.

1. A unique Oct4 interface is crucial for reprogramming to pluripotency.
Esch D, Vahokoski J, Groves MR, Pogenberg V, Cojocaru V, Vom Bruch H, Han D, Drexler HC, Araúzo-Bravo MJ, Ng CK, Jauch R, Wilmanns M, Schöler HR.
Nat Cell Biol. 2013 Feb 3. doi: 10.1038/ncb2680. [Epub ahead of print]
2. A central role for TFIID in the pluripotent transcription circuitry
Pijnappel PW, Esch D, Baltissen MP, Wu G, Mischerikow N, Bergsma AJ, van der Wal E, Han DW, Vom Bruch H, Moritz S, Lijnzaad P, Altelaar AF, Sameith K, Zaehres H, Heck AJ, Holstege FC, Schöler HR, Timmers MH.
Nature, in press

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