Biohelikon: Cell Biology, 2013 1:1

Editorial

Regulation of pluripotency by general transcription factors

Guilai Shi[1*]

[1] Gladstone Institute of Cardiovascular Disease, Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94158, USA

[*] Corresponding author, Email: guilai.shi@gladstone.ucsf.edu

Transcription factor II D (TFIID) is a kind of general transcription factors, and plays critical role in transcription initiation by RNA polymerase II (Pol II). It is composed of TATA binding protein (TBP) and several TBP-associated factors (TAFs). Although its role in transcription is well studied, it is not clear whether it has tissue- or development-specific function. Pijnappel et al. identified the role of TFIID in the regulation of embryonic stem cell (ESC) identity, thereby enriching our understanding of the multifaceted functions of TFIID and also the mechanisms that govern ESC fate [1] .

ESCs have two characteristics: self-renewal and pluripotency, which make them undergo an unlimited number of divisions, while still keep the capacity to differentiate into any cell type of a mature organism. The seminal work of Boyer et al. indicated that ESC identity is regulated by the core transcriptional regulatory circuitry, which is consisted of Oct4, Sox2 and Nanog [2] . The following studies added other ESC-specific transcription factors to this circuitry, like Klf4, Esrrb etc. [3-4] . However, it was unknown if general cellular processes (like epigenetic modification or basal transcriptional machinery) involve in ESC fate regulation. Recently, several epigenetic enzymes have been demonstrated to regulate ESC fate, including Jmjd1a, Jmjd2c, SetDB1, MOF and Wdr5 [5-8] . Although Chia et al. found that knockdown of TAF2, 7 and 12 can induce human ESC differentiation through large-scale screening, they did not examine the role of these TAFs in ESCs further [9] . Another TAF (TAF3) was shown to be required for endoderm lineage differentiation in mouse ESCs, but not for self-renewal [10] . Therefore, there is no solid evidence to show that TFIID plays key role in regulating ESC identity before Pijnappel et al.'s work.

By comparing protein levels of TAFs between mouse ESCs and somatic cells, Pijnappel et al. found that mouse ESCs have higher TAF5 and 6 protein levels. They further showed that human ESCs and induced pluripotent stem cells (iPSCs) also have higher protein levels for several TAFs. When knockdown of these TAFs in mouse ESCs, most knockdown induce differentiation of mouse ESCs, except TAF7 and 8, indicating that the role of TAFs in ESC fate regulation is limited to certain members. The authors also confirmed that the effect of TAFs is not related to Pol II activity.

How TAFs regulate ESC identity? To solve this problem, the authors established two independent stable TAF5 or control knockdown ESCs, and found that TAF5 knockdown decrease pluripotent gene expression, but increase ectodermal and mesodermal lineage gene expression. Chromatin immunoprecipitation (ChIP) results showed that TAF5 knockdown causes decreased binding of TAF1 and TBP to pluripotent gene promoters, but increased binding to lineage gene promoters, consistent with their expression pattern. Moreover, core pluripotent transcription factors can also bind to TAF4 enhancer, which has higher activity in ESCs, implying a feed-forward loop between TAFs and core pluripotent transcription factors.

Besides the role in maintaining pluripotency, the effect of TAFs in regaining pluripotency is also studied. Knockdown of several TAFs significantly reduces reprogramming efficiency of mouse embryonic fibroblasts (MEFs), while over-expression of several TFIID subunits promotes this process. Among these TAFs, over-expression of TAF4 has most significant effect, and can also promote reprogramming of human fibroblasts. However, TFIID alone cannot reprogram somatic cells.

Pijnappel et al.'s findings show that high levels of TFIID are essential to induce and maintain the transcriptional program of pluripotent cells for the first time. Although the authors did not know why pluripotent cells have this TFIID dependency, they proposed a hypothesis that the core promoter sequences of key pluripotency genes are inefficient binders of TFIID, which is remedied by higher TFIID level. It is worth to test this hypothesis by engineering the promoter sequences of key pluripotency genes and manipulating TFIID level. Another way is to find more contexts where higher TFIID level make up weaker recruiting ability of promoter sequences.

Another remaining question is how TFIID promotes reprogramming. One possibility is that TFIID helps establishment of pluripotent transcriptional regulatory circuitry in partially reprogrammed cells. The authors proposed another possibility that TFIID enable fibroblasts to cross the epigenetic energy barriers for resetting gene expression of the pluripotent state, like chromatin regulatory factors. If so, TFIID may also promote trans-differentiation between different lineages, which needs to be tested further.

Conclusion

In this paper, the authors only examined the function of part of TFIID subunits in induction and maintenance of pluripotency, as proof of concept. However, it is not very clear what's the function of each TAF and their interaction in these processes, which needs to be explored further.

References

1. Pijnappel WW, Esch D, Baltissen MP, Wu G, Mischerikow N, et al.: A central role for TFIID in the pluripotent transcription circuitry. Nature 2013, 495: 516-519
2. Boyer LA, Lee TI, Cole MF, Johnstone SE, Levine SS, et al.: Core transcriptional regulatory circuitry in human embryonic stem cells. Cell 2005, 122: 947-956
3. Chen X, Xu H, Yuan P, Fang F, Huss M, et al.: Integration of external signaling pathways with the core transcriptional network in embryonic stem cells. Cell 2008, 133: 1106-1117
4. Kim J, Chu J, Shen X, Wang J, Orkin SH: An extended transcriptional network for pluripotency of embryonic stem cells. Cell 2008, 132: 1049-1061
5. Ang YS, Tsai SY, Lee DF, Monk J, Su J, et al.: Wdr5 mediates self-renewal and reprogramming via the embryonic stem cell core transcriptional network. Cell 2011, 145: 183-197
6. Bilodeau S, Kagey MH, Frampton GM, Rahl PB, Young RA: SetDB1 contributes to repression of genes encoding developmental regulators and maintenance of ES cell state. Genes Dev 2009, 23: 2484-2489
7. Li X, Li L, Pandey R, Byun JS, Gardner K, et al.: The histone acetyltransferase MOF is a key regulator of the embryonic stem cell core transcriptional network. Cell Stem Cell 2012, 11: 163-178
8. Loh YH, Zhang W, Chen X, George J, Ng HH: Jmjd1a and Jmjd2c histone H3 Lys 9 demethylases regulate self-renewal in embryonic stem cells. Genes Dev 2007, 21: 2545-2557
9. Chia NY, Chan YS, Feng B, Lu X, Orlov YL, et al.: A genome-wide RNAi screen reveals determinants of human embryonic stem cell identity. Nature 2010, 468: 316-320
10. Liu Z, Scannell DR, Eisen MB, Tjian R: Control of embryonic stem cell lineage commitment by core promoter factor, TAF3. Cell 2011, 146: 720-731