Novel system reveals mechanisms of pluripotency transition

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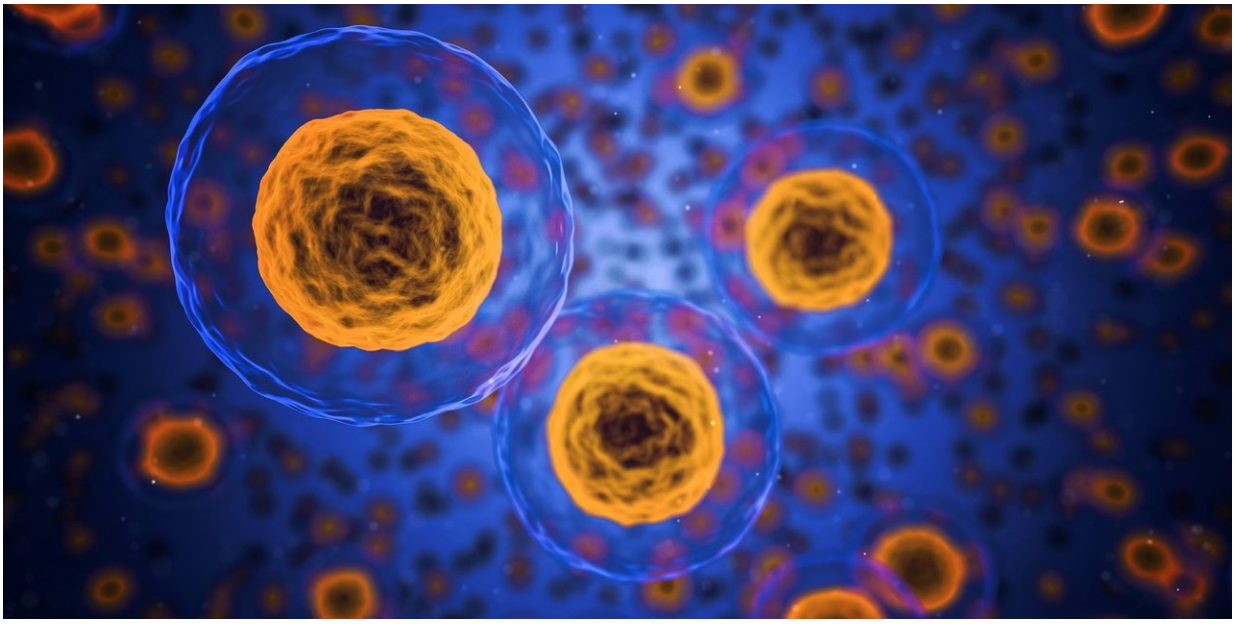

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In a study published online in *Nature Cell Biology* on May 11, scientists from Guangzhou Institute of Biomedicine and Health (GIBH) of the Chinese Academy of Sciences established a novel and efficient system for non-integrated mouse Primed pluripotency to Naive pluripotency Transition (PNT) and elaborated the new mechanisms underlying the PNT process.

Mouse embryonic stem cells exist in two unique pluripotent states, Naive state and Primed state. PrimPNT represents the reverse of the embryonic development stage from post-implantation to pre-implantation, which needed to overcome some important epigenetic barriers. In the previous reports, PNT usually required the infection of transcription factors by viral vector, which is cumbersome in operation and low in efficiency, hampering its widely application in the field. In addition, the underlining mechanisms for PNT remain to be further clarified.

To address the above issues, the researchers established a PNT system. They first screened a series of growth factors and found that BMP4 was capable to induce PNT in mice. By screening a compound library, they then identified two small molecule inhibitors, EPZ6438 and EPZ5676, could improve PNT efficiency synergistically. Based on these, the researchers established a PNT induction system with more than 80% efficiency within eight days.

Importantly, the withdrawal of the BMP signal will totally abolish the PNT process, thus they termed this newly established PNT system as BiPNT (BMP induced PNT).

Besides, the researchers depicted the chromatin accessibility dynamics during BiPNT by using RNA-seq and ATAC-seq (chromatin transposase accessibility sequencing), and proved that, BMP4, the most critical diver factor in BiPNT, inhibited the opening of chromatin loci of differentiation related genes and promoted the opening of chromatin loci of naive pluripotent related genes.

They identified for the first time transcription factors Zbtb7a and Zbtb7b, as novel targets of BMP4, could regulate PNT by affecting chromatin remodeling. ChIP-seq experiment further proved that Zbtb7a directly activates the expression of naive pluripotency genes such as

Esrrb, Klf2 and Nr5a2, by binding to the upstream regulate elements in the chromatin, thus regulates the occurrence of PNT.

This study improved the PNT transition technic and revealed novel mechanisms for understanding the PNT process. The BiPNT system provides a wonderful paradigm for studying the mechanism of how extracellular signal mediated cell fate transition. In addition, this study offered a valuable reference for the acquisition of naive human embryonic stem cells.

Cell reprogramming and cell fate transition are determined by sophisticated signals transduction and epigenetic regulation. The underlying mechanism and working models for these processes are core issues in the field of cell biology.

More information: Shengyong Yu et al. BMP4 resets mouse epiblast stem cells to naive pluripotency through ZBTB7A/B-mediated chromatin remodelling, *Nature Cell Biology* (2020). DOI: 10.1038/s41556-020-0516-x

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