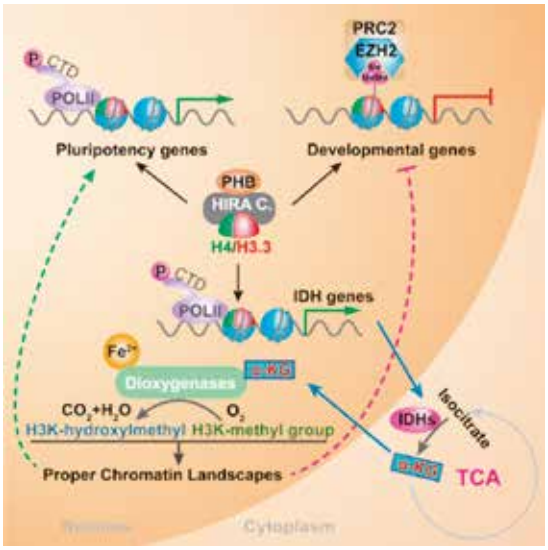
PHB Associates with HIRA Complex to Control an Epigenetic-Metabolic Circuit in Human ESCs

It is well known that embryonic stem cells can self-renewal unlimitedly and differentiate into all cell types of an organism *in vitro*, having broad applications for future organ regeneration and cell replacement therapy. However, there are still many questions about the molecular regulation of self-renewal and pluripotency in hESCs. Therefore, it is important to study the mechanism by which hESCs maintain their own characteristics.

A research group led by Dr. JIN Ying from the Institute of Health Sciences(HIS), Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS) and School of Medicine, Shanghai Jiao Tong University, revealed the importance of prohibitin (PHB) as a new member of the HIRA Complex in the maintenance of self-renewal of human embryonic stem cells (hESCs). The work entitled "PHB Associates with the HIRA Complex to Control an Epigenetic-Metabolic Circuit in Human ESCs" was published online in the journal of *Cell Stem Cell* on December 8, 2016.

Under Dr. JIN Ying's supervision, Ph.D. candidate ZHU Zhexin screened factors required for hESC self-renewal maintenance using a genome-wide transcription factor siRNA library, and identified prohibitin (PHB) as an essential factor for self-renewal of hESCs. Mechanistically, the team found that PHB forms protein complexes with HIRA, a histone H3.3 chaperone, and stabilizes the protein levels of HIRA complex components. PHB and HIRA act together to control global deposition of histone H3.3 and gene expression in hESCs. Of particular note, PHB and HIRA regulate the chromatin architecture at the promoters of isocitrate dehydrogenase genes to promote transcription and, thus, production of a-ketoglutarate, a key metabolite in the regulation of ESC fate.

Their study shows that PHB has an unexpected nuclear role in hESCs and reveals for the first time that HIRA complex and H3.3 play important roles in the transcription of IDH and production of a-ketoglutarate, an important cofactor of dioxygenases. Thus, PHB acts together with HIRA complexes to control a H3.3 related epigenetic-metabolic circuitry in hESCs, maintaining normal chromatin structure and hESC identity.



Based on a genome-wide siRNA screen, JIN and colleagues identify PHB as a key factor in hESC self-renewal. PHB forms a complex with HIRA to regulate deposition of histone H3.3 and expression of a range of genes, including some related to metabolic circuitry. (Image by Prof. JIN Ying's group)

This study was supported by grants of the Strategic Priority Research Program of CAS (XDA01010102 and XDB19020100), the Ministry of Science and Technology of China (2016YFA0100100 and 2013CB966801), and the National Natural Science Foundation of China (91419309).

Contact:

Dr. JIN Ying
Email: yjin@sibs.ac.cn
Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences and Shanghai Jiao Tong University School of Medicine