

Report of “Research Award of Oral Sciences”

Department: Histology and Oral Histology

Name: Yang Di

Title: Histone demethylase Jmjd3 and Utx regulate osteoblast differentiation and bone mineralization

1. Aim of research and results obtained (Approximately 800 words):

Alteration of methylation status of lysine 27 on histone H3 (H3K27) associates with dramatic changes in gene expression in response to various differentiation signals. Demethylation of H3K27 is controlled by specific histone demethylases including Jumonji domain containing 3 (Jmjd3) tetratricopeptide repeat X chromosome (Utx). However, the role of Jmjd3 and Utx in osteoblast differentiation remains unknown. In this study, expressions of Jmjd3 and Utx increased during osteoblast differentiation in MC3T3-E1 cells and primary osteoblasts. GSK-J1, a potent inhibitor of H3K27 demethylase, increased the levels of trimethylated H3K27 (H3K27me3) and decreased the expressions of Runx2 and Osterix and ALP activity in MC3T3-E1 cells. Stable knockdown of Jmjd3 and Utx by shRNA attenuated osteoblast differentiation and decreased ALP activity, calcium content, and bone-related gene expressions. Silencing of Jmjd3 and Utx increased the level of H3K27me3 on the promoter regions of Runx2 and Osterix and decreased the promoter activities of Runx2 and Osterix. Taken together, our present results propose that Jmjd3 and Utx play important roles in osteoblast differentiation by controlling the expression of Runx2 and Osterix.

2. Self-evaluation of research achievement:

Under the support of Research Award of Oral Sciences, our research project went on well and we demonstrated that histone demethylase Jmjd3 and Utx regulate osteoblast differentiation via transcriptional factors Runx2 and Osterix.

We already published part of these data on the Journal of Biological Chemistry. The other part of these data has been submitted to the Journal of Cellular Biochemistry and now is on revising.

3. Meeting presentation (First author only)

- 1) Di Yang, Hirohiko Okamura, Tatsuji Haneji. Involvement of Jmjd3 in osteoblast differentiation, Bone and Cartilage: from development to human diseases, Cold Spring Harbor Conferences Asia, Suzhou, China, 2012-06-13 (oral)
- 2) Di Yang. Involvement of Jmjd3 in osteoblast differentiation, Tokushima Bioscience Retreat, 香川県 オリビアン小豆島, 2012-09-14 (oral)
- 3) Di Yang, Hirohiko Okamura, Tatsuji Haneji. Involvement of Jmjd3 in osteoblast differentiation, 日本解剖学会第 67 回中国四国支部学術集会, 山口県, 2012-09-21 (oral)
- 4) Di Yang, Hirohiko Okamura, Tatsuji Haneji. Involvement of Jmjd3 in osteoblast differentiation, Asean plus and Tokushima joint international conference, Yogyakarta, Indonesia, 2012-12-06 (poster)
- 5) Di Yang. Epigenetic regulation of osteoblast differentiation by Jmjd3, 骨と Ca クラスタターミニトリート, 淡路島, 2013-02-02 (oral)
- 6) Di Yang, Hirohiko Okamura, Jumpei Teramachi, Tatsuji Haneji. The regulation of osteoblast differentiation by Jmjd3, 第 118 回日本解剖学会総会全国学術集会, 香川県, 2013-03-30 (oral)
- 7) Di Yang. Histone demethylase Jmjd3 regulates osteoblast differentiation via transcription factor Osterix, Tokushima Bioscience Retreat, 香川県, オリビアン小豆島, 2013-09-20 (oral)
- 8) Di Yang. Histone demethylase Jmjd3 regulates osteoblast differentiation via transcription factor Osterix, 先端歯学スクール 2013, 東京, 2013-09-26 (oral)
- 9) Di Yang, Hirohiko Okamura, Jumpei Teramachi, Tatsuji Haneji. Histone demethylase Jmjd3 regulates osteoblast differentiation via transcription factor Osterix, 日本解剖学会第 68 回中国四国支部学術集会, 鳥取県, 2013-10-20 (oral)
- 10) Di Yang. Histone demethylase Jmjd3 regulates osteoblast differentiation via transcription factors Runx2 and Osterix, 骨と Ca クラスタターミニトリート, 淡路島, 2014-01-31 (oral)
- 11) Di Yang, Hirohiko Okamura, Jumpei Teramachi, Tatsuji Haneji. Histone demethylase Jmjd3 regulates osteoblast differentiation via transcription factor Runx2, 第 119 回日本解剖学会総会全国学術集会, 下野市, 2014-03-29

(oral)

- 12) Di Yang, Tatsuji Haneji. Osteoblast differentiation and histone demethylase Jmjd3, The 11th China-Japan Joint Seminar Histochemistry and Cytochemistry (CJJSHC 2014), 松本市, 2014-09-28 (poster)

4. Journal publication:

- 1) Yang D, Okamura H, Nakashima Y, Haneji T. Histone demethylase Jmjd3 regulates osteoblast differentiation via transcription factors Runx2 and Osterix, *Journal of Biological Chemistry*, 288, 33530-33541, 2013
- 2) Okamura H, Yang D, Yoshida K, Haneji T. Protein phosphatase 2A Ca is involved in osteoclastogenesis by regulating RANKL and OPG expression in osteoblast. *FEBS Letters*, 587, 48-53, 2013
- 3) Okamura H, Yoshida K, Yang D, Haneji T. Protein phosphatase 2A Ca regulates osteoblast differentiation and the expression of Bone sialoprotein and Osteocalcin via Osterix transcription factor, *Journal of Cellular Physiology*, 228, 1031-1037, 2013
- 4) Okamura H, Yang D, Teramachi J, Yoshida K, Haneji T. Reduction of PP2A Ca stimulates adipogenesis by regulating the Wnt/GSK-3 β / β -catenin pathway and PPAR γ expression. *BBA-Molecular Cell Research*, 1843, 2376-2384, 2014
- 5) Yu Y, Yang D, Qiu L, Okamura H, Guo J, Haneji T. Tumor necrosis factor- α induces interleukin-34 expression through nuclear factor- κ B activation in MC3T3-E1 osteoblastic cells, *Molecular Medicine Reports*, 10, 1371-1376, 2014
- 6) Guo J, Yang D, Okamura H, Teramachi J, Ochiai K, Qiu LH, Haneji T. Calcium hydroxide suppresses the virulence of lipopolysaccharide from *Porphyromonas endodontalis* to bone cells, *Journal of Dental Research*, 93, 508-513, 2014
- 7) Shinohara H, Teramachi J, Okamura H, Yang D, Nagata T, Haneji T. Double stranded RNA-dependent protein kinase regulates TNF- α -induced osteoclast formation in vitro and in vivo, *Journal of Cellular Biochemistry* (in press)