Form 8

ABSTRACT OF DISSERTATION

Title	Histone Demethylase Jmjd3 Regulates Osteoblast Differentiation via Transcription Factors *Runx2* and Osterix ヒストンデメチラーゼ Jmjd3 は転写因子 *Runx2* と Osterix を介して骨芽細胞の分化を調節する
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Post-translational modifications of histones including methylation play important roles in cell differentiation. Jumonji domain-containing 3 (Jmjd3) is a histone demethylase, which specifically catalyzes the removal of trimethylation of histone H3 at lysine 27 (H3K27me3). In this study, I examined the expression of Jmjd3 in osteoblasts and its roles in osteoblast differentiation. Jmjd3 expression in the nucleus was induced in response to the stimulation of osteoblast differentiation as well as treatment of bone morphogenetic protein-2 (BMP-2). Either treatment with Noggin, an inhibitor of BMP-2, or silencing of Smad1/5 suppressed Jmjd3 expression during osteoblast differentiation. Silencing of Jmjd3 expression suppressed osteoblast differentiation through the expression of bone-related genes including Runx2, Osterix, osteopontin (OPN), bone sialoprotein (BSP), and osteocalcin (OCN) and inhibited bone formation *in vivo*. Silencing of Jmjd3 decreased the promoter activities of Runx2 and Osterix and increased the level of H3K27me3 on the promoter regions of Runx2 and Osterix. Introduction of the exogenous Runx2 and Osterix partly rescued osteoblast differentiation in the Jmjd3 knockdown cells. The present results indicate that Jmjd3 plays important roles in osteoblast differentiation and regulates the expressions of BSP and OCN via transcription factors Runx2 and Osterix.