The Regulation of Bone Acquisition by mTORC1 Signaling

Thomas Kim, DDS Candidate 2022
Faculty Mentor: Fei Liu DDS, PhD
University of Michigan School of Dentistry

Introduction

Tuberous sclerosis (TSC) is a genetic disorder characterized by the presence of benign congenital tumors in multiple organs and is caused by mutations in one of two genes, called TSC1 and TSC2. Tuberous sclerosis bone dysplasia is characterized by osteosclerotic changes in skeletal and craniofacial bones. In this disease, hyperactivity of mTORC1 (mammalian target of rapamycin complex 1) signaling is implicated. Once the mTORC1 signaling is activated, it can enhance anabolic processes such as protein synthesis. Using transgenic mouse models, literature showed the important but complex roles of Tsc1/mTORC1 signaling in bone homeostasis. Our group previously showed that Tsc1 deletion in neural crest-derived cells results in increased craniofacial bone mass (JBMR 2015)1; however, Tsc1 deletion in osteoblasts results in decreased trabecular bone mass in one-month-old mice (JBMR 2018)2. Thus, the impact of TSC1 activation on the function of different osteoblastic lineage cells and the consequent effect on bone acquisition is still not completely understood.

Objectives

The goal of this study is to systematically investigate and compare the effect of Tsc1 deletion/mTORC1 activation in different osteoblastic lineage cells (osteoblasts vs. osteocytes) on bone acquisition. The hypothesis is that mTORC1 activation by Tsc1 deletion affects bone acquisition in cell lineage-dependent manner.

Methods

Micro-computed Tomography

The femurs of 2-month-old male and female Tsc1Cre;Dmp1-Cre (KO/WT-Cre), Tsc1flox;Dmp1-Cre (Cre/WT-Cre), and Tsc1flox/Dmp1flox (Control) mice as well as 2-month-old female Tsc1flox;Cre (KO/Cre) and Tsc1flox/Dmp1flox (Control) mice were scanned and reconstructed via Micro-CT. Bone morphological parameters were analyzed in both cortical and trabecular bones.

Statistics

Student t-test was used when there were two groups. One way ANOVA followed by Dunnett’s multiple comparison test was used when there are three groups. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, and ns means “no statistical significance”.

Results

1. Tsc1 deletion in osteoblasts led to increased femoral and tibial bones in both cortical and trabecular compartments to the same extent, indicating that osteocytes may be the major mediator of this effect.


Figure 1: Tsc1 deletion in osteoblasts using Osterix-Cre led to decreased bone mass in mice.

Figure 2: Tsc1 deletion in osteocytes using Dmp1-Cre led to decreased bone mass in female mice.

Table 1: comparison of the effects of Tsc1 deletion in osteoblasts vs. osteocytes and male vs female. * means significant difference between KO and respective control; and ** means significant difference (p<0.05) and *** means a trend in difference (p=0.09) between male and female within Dmp1-Cre groups.

Conclusions

1. Tsc1 deletion in osteoblasts and osteocytes led to increased femoral bone mass in both cortical and trabecular compartments to the same extent, indicating that osteocytes may be the major mediator of this effect.

2. The female mice appeared to have larger increase in bone mass in response to Tsc1 deletion, which can be accounted for by the larger periodical expansion in the cortical bone and the larger increase in trabecular number in trabecular bone.

Acknowledgements & References

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