MOLECULAR MECHANISMS ALTERING SKELETAL DEVELOPMENT AND HOMEOSTASIS IN TS65DN DOWN SYNDROME MICE

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Down syndrome (DS) is caused by three copies of human chromosome 21 (HSA21) and results in abnormal craniofacial and appendicular bone phenotypes. The Ts65Dn mouse model of DS contains three copies of nearly half of the genes found on HSA21, and exhibits craniofacial skeletal phenotypes similar to those observed in humans with DS. We recently demonstrated abnormalities in the development and homeostasis of the appendicular skeleton of Ts65Dn mice. Femurs from trisomic mice exhibit alterations in trabecular bone architecture and overall bone strength. Furthermore, bone formation rates were found to be significantly reduced, suggesting trisomy impacts bone development and maintenance in Ts65Dn mice, and by extension humans with DS. *DYRK1A* is triplicated in both humans with DS and Ts65Dn mice and its protein acts as a kinase critical during development. Dyrk1A negatively regulates the nuclear localization and activation of Nfatc, a transcription factor critical to signaling pathways associated with cell proliferation and bone development, and is overexpressed in the E9.5 Ts65Dn mandible precursor. We hypothesize that the previously documented Ts65Dn bone phenotype originates during embryonic development, and the presence of an extra copy of *Dyrk1a* contributes to the abnormal bone phenotype observed in Ts65Dn mice and humans with DS. To test our first hypothesis, analysis of the cartilage template and early bone precursor is being conducted on the femurs from embryonic day 17.5 trisomic and euploid embryos. To implicate the involvement of *Dyrk1a* in the DS bone phenotype, Ts65Dn mice are being treated with a known *Dyrk1a* inhibitor, EGCG, to determine if correcting the functional expression of *Dyrk1a* impacts the development of the Ts65Dn postnatal bone phenotype. Understanding the molecular mechanisms underlying DS bone phenotypes may help improve the quality of life for individuals with DS and provide viable options for the treatment of osteoporosis.

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