

Evaluation of osteoclastogenesis in the Ts65Dn Down Syndrome Mouse Model

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Down Syndrome (DS) affects ~1 in 700 live births and is caused by trisomy of human chromosome 21 (Hsa21). DS is characterized by a wide spectrum of phenotypes including cognitive and skeletal abnormalities that affect all individuals with DS. To study these phenotypes, we utilize the Ts65Dn mouse model, which contains three copies of approximately half the gene orthologous found on Hsa21 and exhibits similar phenotypes as found in humans with DS. Individuals with DS and Ts65Dn mice have deficits in bone mineral density (BMD), bone architecture, and bone strength. Three copies of *DYRK1A*, a serine-threonine kinase encoded on Hsa21, has been linked to deficiencies in bone homeostasis in DS mouse models and individuals with DS. *DYRK1A* is thought to act via NFATc1, a master regulator of osteoclastogenesis. Epigallocatechin-3-gallate (EGCG), a polyphenol found in high concentrations in green tea, is a known inhibitor of *DYRK1A* activity. We propose that the DS bone phenotype arises from an increase in osteoclastogenesis and/or maturation which results in increased bone resorption and disrupted bone homeostasis. We hypothesize that treatment of the mice during adolescence with 100 mg/kg/day EGCG would result in normalization of osteoclast numbers in trisomic mice to that of the controls. Osteoclast precursors from femur and spleen were isolated from 8-10 week old mice treated with 100 mg/kg/day EGCG or water from three weeks of age onwards. The cells were grown in the presence of M-CSF & RANK-L to promote osteoclast differentiation. Following 3 weeks in culture, the cells were fixed, TRAP stained, and multinucleated osteoclasts from control and Ts65Dn treated and untreated mice were counted.

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