

Effects of the Calcineurin/NFAT Pathway in Skeletal Abnormalities Associated with Down Syndrome

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Down Syndrome (DS) is a genetic disorder caused by trisomy of human chromosome 21 (Hsa21). DS phenotypes include cognitive impairment, craniofacial abnormalities, and skeletal deficiencies. The Ts65Dn mouse model exhibits similar phenotypes as found in humans with DS, including deficits in skeletal bone. Over-expression of *DYRK1A*, a serine-threonine kinase encoded on Hsa21, has been linked to deficiencies in DS bone homeostasis. Calcineurin/NFAT pathway plays a role in bone homeostasis by regulating osteoblastogenesis and osteoclastogenesis. *DYRK1A* was found to regulate calcineurin/NFAT signaling to block transcriptional activity, thereby reducing calcineurin/NFAT transcriptional activity. Epigallocatechin-3-gallate (EGCG), an aromatic polyphenol found in green tea, is a known inhibitor of *DYRK1A* activity. Normalization of *DYRK1A* activity by EGCG may have the potential to regulate bone homeostasis, by increasing bone mineral density (BMD) and bone strength. In earlier our work, EGCG treatment of 30mg/kg/day, has been shown to improve skeletal deficits, however, the mechanism remains unknown. We hypothesize that EGCG is involved in the calcineurin/NFAT pathway. To test our hypothesis we will use cyclosporine A (CsA), an immunosuppressant that perturbs the calcineurin/NFAT pathway. Previous studies show that daily administration of high concentration CsA will result in significant bone loss. Three-week old euploid and trisomic Ts65Dn mice receive 30mg/kg/day of CsA or vehicle for 3 weeks. In addition, mice will receive EGCG or water. At six weeks of age, BMD, bone strength, as well as architecture of the cortical and trabecular bone are assessed in extracted femurs. We expect that CsA given to euploid mice exhibit bone phenotypes similar to trisomic mice. Whereas euploid mice given CsA and EGCG might display bone phenotypes similar to euploid given only the vehicle. Provided that we are able to observe our expected results, it may indicate that EGCG is involved in the calcineurin/NFAT pathway. Our work is important to understand how EGCG may affect DS phenotypes as the EGCG is translated to human use.

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