Mandibular and Neural Crest Cell Deficits Seen in TsDn65 Down Syndrome Mouse Model Rescued By Green Tea Polyphenol, EGCG

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Down Syndrome (DS) is caused by trisomy of the human chromosome 21 (Hsa21) and occurs in ~1 of every 700 births. DS is distinguished by over 80 phenotypic abnormalities including skeletal deficits and craniofacial phenotypes characterized by a flattened skull, slanted eyes, and a smaller mandible. To study these abnormalities, we utilize the Ts65Dn DS mouse model containing a triplication of approximately half of the gene homologues found on Hsa21 and mirrors the skeletal and mandibular phenotypes observed in DS. In Ts65Dn mice, the origin of the mandibular deficits were traced to a reduction in size of the 1st branchial arch (BA1), the developmental precursor to the mandible, occurring at embryonic day 9.5 (E9.5). At E9.5, we observe a lack of proliferation and migration of neural crest cells (NCC) from the neural tube (NT) into the BA1, causing a reduced BA1. We hypothesize that an overexpression of *Dyrk1a*, a Hsa21 homologue, contributes to the mandibular deficit seen in E9.5 Ts65Dn embryos. We propose that EGCG, a green tea polyphenol, will inhibit DYRK1a activity, rescuing the BA1 deficit. To test our hypothesis, Ts65Dn mothers were treated with EGCG from E0-E9.5 and sacrificed to retrieve the E9.5 embryos. Our results from unbiased stereological assessments show that E0-E9.5 EGCG *in vivo* treatment has the potential to increase NCC number, BA1 volume, and embryo volume of trisomic embryos. This data provide preclinical testing for a potential therapy of DS craniofacial disorders, which may extend to treating bone deficits in DS and osteoporosis.

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