

Correction of Craniofacial Deficits using Epigallocatechin-3'-gallate Treatment in a Down Syndrome Mouse Model

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Down syndrome (DS) is caused by trisomy of human chromosome (HSA21). Individuals with DS display distinct craniofacial abnormalities including an undersized, dismorphic mandible which leads to difficulty with eating, breathing, and swallowing. Using the Ts65Dn DS mouse model (three copies of ~50% HSA21 homologs), we have traced the mandibular deficit to a neural crest cell (NCC) deficiency and reduction in first pharyngeal arch (PA1 or mandibular precursor) at embryonic day 9.5. Previous studies have shown that this deficit is caused when NCC fail to migrate from the neural tube to populate the PA1 and fail to proliferate in the PA1. At E9.5, Dyrk1A, a triplicated DS candidate gene, is overexpressed in the PA1 and may cause the NCC and PA1 deficits. We hypothesize that treatment of pregnant Ts65Dn mothers with Epigallocatechin-3'-gallate (EGCG), a known Dyrk1A inhibitor, will correct NCC deficits and rescue the undersized PA1 in trisomic E9.5 embryos. To test our hypothesis, we treated pregnant Ts65Dn mothers with EGCG, where embryos received treatment from either E7-E8 or E0-E9.5. Our preliminary study found variable increases in PA1 volume and NCC number between treatment regimens, with several treatment groups indicating EGCG treatment has the potential to rescue the NCC deficit in the mandibular precursor. We found an increase in NCC number and PA1 volume with E7-E8 EGCG treatment in 21-24 somite embryos from trisomic mothers and in euploid embryos from euploid mothers treated from E0-E9.5. With EGCG treatment, we also observed a decrease in the average somite number of embryos from trisomic mothers, but an increase in those mothers' average litter size. This study is important because it helps define the specific dosage and timing of EGCG and how it may affect specific DS phenotypes. These findings provide preclinical testing for a potential therapy for craniofacial disorders linked to DS.