MOLECULAR BASIS AND MODIFICATION OF A NEURAL CREST DEFICIT IN A DOWN SYNDROME MOUSE MODEL

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Trisomy 21 occurs in 1/700 live births and leads to phenotypes associated with Down syndrome (DS), including craniofacial dysmorphology and a small mandible. Ts65Dn mice are trisomic for approximately half the genes on human chromosome 21 and display DS-like craniofacial anomalies. Cells cultured from Ts65Dn and euploid 1st pharyngeal arch (PA1) and neural tube (NT) tissues were used to analyze the effects of genetic dysregulation on cell proliferation and migration. *In vitro* studies revealed a proliferation deficit in trisomic PA1 and migration deficits from trisomic NT originating at embryonic day 9.5 (E9.5). *DYRK1A* is a gene thought to be involved in DS craniofacial development and we hypothesized that dysregulation of *Dyrk1a* contributes to altered craniofacial development in Ts65Dn mice. We also hypothesized that Dyrk1a agonists could be used to ameliorate this phenotype. To test our hypotheses, we quantified expression of *Dyrk1a* using qPCR. At E9.5, *Dyrk1a* is upregulated in Ts65Dn as relative to euploid PA1. We also showed that cell proliferation and migration could be returned to near euploid levels with the green tea polyphenol epigallocatechin gallate (EGCG) and harmine (known Dyrk1a inhibitors) *in vitro*. To further test our hypothesis, pregnant Ts65Dn and euploid mothers were treated with EGCG on E7 and E8 and E9.5 trisomic and euploid embryos were assessed for embryonic volume, PA1 volume, and NCC number. Preliminary evidence suggests *in vivo* treatment leads to an increase in embryonic volume, PA1 volume, and NCC number in both euploid and trisomic embryos. Trisomic EGCG-treated embryos had similar PA1 volumes and NCC numbers to euploid embryos treated with PBS. Gene expression analysis of EGCG-treated NCCs is currently underway to better understand the effects of EGCG in these studies. Our results provide information about the molecular basis of DS craniofacial abnormalities and may lead to evidenced-based therapeutic options.

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