Down Syndrome Trophoblasts from Induced Pluripotent Stem Cells Display Differentiation Defects

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Down Syndrome (T21) pregnancies are at an increased risk of adverse outcomes resulting from placental insufficiency, yet the etiology behind these defects is unknown. Additionally, T21 placental explant cultures display defects in fusion and differentiation into multinucleated syncytiotrophoblasts (STB). However, placental explants are derived from mid- to late- term placental tissue and offer limited potential to functionally explore mechanistic differences in T21 trophoblast differentiation potential. We hypothesize that aberrant development of T21 placental trophoblast cells occurs early in gestation during peri-implantation and that differentiation of induced pluripotent stem (iPS) cells may serve as an appropriate model system to study peri-implantation T21 trophoblasts. Here, we report that T21 trophoblasts can be modeled in vitro by T21 iPS cells following exposure to BMP4, a TGFβ inhibitor (A83-01), and a fibroblast growth factor receptor inhibitor (PD173074). Directed differentiation of a T21 and an isogenic euploid control (D21) iPS cell line from the same donor results in expression of putative trophoblast lineage markers, GATA3 and TFAP2C, by immunofluorescence (IF), and cells secrete human chorionic gonadotropin beta, a hallmark of STB. Differentiated iPS cells can be further separated into mononucleated cytotrophoblast-like cells and STB-like cells based on qPCR analysis of each population. Following differentiation (n=3), T21 cells exhibit reduced cell fusion compared to D21. Furthermore, expression of putative STB markers, *CGB, ERVW-1,* and *GCM1* are reduced in T21 compared to D21. Future studies characterizing the global transcriptome of 6 age- and sex- matched iPS cell lines will aim to identify a mechanism by which STB differentiation is disrupted in T21 placentas. This work is supported by a Sie fellowship from the Linda Crnic Institute for Down Syndrome.