Role of astroglia in Down's syndrome revealed by patient-derived human-induced pluripotent stem cells.

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Public Summary:
Down's syndrome (DS), caused by trisomy of human chromosome 21, is the most common genetic cause of intellectual disability. Here we use induced pluripotent stem cells (iPSCs) derived from DS patients to identify a role for astrocytes in DS pathogenesis. DS astroglia exhibit higher levels of reactive oxygen species and lower levels of synaptogenic molecules. Astrocyte-conditioned medium collected from DS astroglia causes toxicity to neurons, and fails to promote neuronal ion channel maturation and synapse formation. Transplantation studies show that DS astroglia do not promote neurogenesis of endogenous neural stem cells in vivo. We also observed abnormal gene expression profiles from DS astroglia. Finally, we show that the FDA-approved antibiotic drug, minocycline, partially corrects the pathological phenotypes of DS astroglia by specifically modulating the expression of S100B, GFAP, inducible nitric oxide synthase, and thrombospondins 1 and 2 in DS astroglia. Our studies shed light on the pathogenesis and possible treatment of DS by targeting astrocytes with a clinically available drug.

Scientific Abstract:
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