

Down Syndrome's Models of Human Nondisjunction and Mouse Models

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ABSTRACT

Trisomy of human chromosome 21 (Hsa21) and Down syndrome (DS) is challenging to model in mice. Hsa21 (Orthologs) genes map to segments called Mmu16, Mmu17, and Mmu10. For DS Ts65Dn was the first viable segmental trisomy mouse model and it is a partial trisomy currently popular in preclinical evaluations of drugs for cognition in DS. Ts65Dn a limitations are as follows: (i) it is trisomic for 125 human protein-coding orthologs, but only 90 of these are Hsa21 orthologs (ii) it lacks trisomy for ~75 Hsa21 orthologs.

KEYWORDS: Mouse chromosome abnormalities, Mouse chromosomes, Down syndrome, Genes

INTRODUCTION

Leading cause of fetal death in our species is chromosomal aneuploidy. 50% of spontaneous abortions are chromosomally aneuploid with trisomies 50% of the abnormal abortions. Condition is result of malsegregation of chromosome 21 in meiosis in either oogenesis or spermatogenesis. Down syndrome (DS) is caused by mostly trisomy 21 and common single cause of mental retardation. Chromosomes are kept strictly constant by mitosis in the diploid body cells as well as in the mitotic germ line. It is reduced to half by meiosis in the generation of female or male haploid germ cells. Each chromosome consists of two sister chromatids, which stem from the preceding round of replication and are identical throughout their length during mitosis. Segregation of chromosomes in mitosis as well as bivalents in meiosis are critically depends on their bipolar spindle attachment.

Mitotic errors aren't associated with maternal age and show no preference in the parental origin of the duplicated chromosome 21. Mosaicism with a normal cell line occurs in about 2%-4% of Down Syndrome newborns. The majority of cases resulted from a trisomic zygote with mitotic loss of one chromosome, it showed when DNA polymorphism analysed in mosaic trisomy 21 probands. Number of laboratories being pursued to create mice with three copies of a defined chromosomal segment using chromosome engineering and they have provided refined genetic

models for assessment of hypotheses concerning critical genes versus destabilising effects of trisomy.

Second segmental trisomy 16 model, Ts1Cje, arose as a fortuitous translocation of chromosome 16 in a transgenic mouse line. These mice are having dosage imbalance for a subset of the segment triplicated in Ts65Dn, corresponding to a human chromosome 21 region. Other mouse models, including Ts16, Ts1Cje and Ms1Cje, Ts1Rhr and MTs1Rhr, Ts1Yah and Ms2Yah, and Dp(10)1Yey/+; Dp(16)1Yey/+; Dp(17)1Yey/+ models have been previously recruited for DS.

Molecular quantitative analyses indicated that trisomy is inducing an overexpression for a large part of the triplicated genes and deregulates also pathways involving non HSA21 genes. Together with the physiological description of murine models overexpressing orthologous genes, these data have allowed to elaborate hypotheses on the cause of cognitive impairment. From these hypotheses and using murine models it is now possible to assess the efficiency of various therapeutic strategies. A recent paper [16] reviewed these new perspectives starting from the strategies targeting the level of HSA21 RNAs or HSA21 proteins; then it described methods targeting activities either of proteins involved in cell cycle pathways or of proteins controlling the synaptic plasticity. It is promising that strategies targeting specific genes or specific pathways are already giving positive results.

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