Neuron Differentiation in Mouse ES Cells Containing a Single Human Chromosome 21: An in Vitro Model of Neurogenesis in Down's Syndrome

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Neuro-degeneration early in fetal development in the brains of Down syndrome (DS) patients is proposed to result in the apparent neuropathological abnormalities, and to contribute to the phenotypic character such as mental retardation and premature development of the pathologies of Alzheimer disease, those being the most common phenotype in DS. In order to dissect and identify the aberrant and specific genes manifested as developmentally associated in the early differentiating DS neurons, we have utilized an in vitro neuronal differentiation system of mouse ES cells containing a single human chromosome 21 (TT2F/hChr21) as a model of DS neuronal development, compared with TT2F parental ES cells as a control.

To understand the molecular mechanism underlying the cause of phenotypic abnormalities in the DS brain, we have utilized an *in vitro* neuronal differentiation model of TT2F mouse ES cells containing a single human chromosome 21 (hChr21) to study neuron development and neuronal differentiation by microarray containing 15K developmentally expressed cDNAs. We have made use of multiple gene expression patterns that are more powerful in defining individual characteristics and predicting outcomes than any single gene expression pattern. Statistical tree-based classification systems provide a framework for assessing multiple patterns selecting those that are most capable of resolving the biological heterogeneity. Defective neuronal differentiation in the presence of extra hChr21 was evidenced and the manifestation primarily was affected in post-transcriptional and translational modification in different stages of neuronal differentiation. Hierarchical clustering patterned specific gene expression of hChr21 gene dosage effects on neuron outgrowth, migration and differentiation. Revealed underlying mechanism in the failure of genetic information between the genome and the proteoimes during neuron differentiation may elucidate the discrepancy of hChr21 gene dosage effects but selectively imbalanced particular gene functions in other chromosomes, however.

The paired protein extracts from TT2F and TT2F/hChr21 cells at several stages of neuronal differentiation were subjected to 2-DE protein separation followed by MALDI-TOF-MS to identify the proteins differentially expressed between TT2F and TT2F/hChr21 cells. We provide here a novel set of specific gene products altered in early differentiating DS neuronal cells, which is different from that identified in adult or fetal brain with DS. The aberrant protein expression in early differentiating neurons, due to the hChr21 gene dosage effects or chromosomal imbalance, may affect the neuronal outgrowth, proliferation and differentiation implying the developmental abnormalities in neural patterning, eventually leading to formation of a suboptimal functioning neuronal network in DS.

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