

Systems biology and Down syndrome mouse models

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Because of the number of genes involved and the complexity of the phenotype, Down syndrome (DS) requires a systems biology approach. We are combining bioinformatics and experiments to characterize pathways relevant to learning/memory that are perturbed in DS and to identify the chromosome 21 genes responsible for the perturbations. For each chr21 protein, pathways are defined by identifying (1) mammalian protein interactions from curated databases and the primary literature, and (2) orthologous protein interactions in model organisms. We also extract chr21 protein information from large scale functional genomics and proteomics datasets. All data are compiled in the chr21/DS gene function database (<http://chr21db.cudenver.edu>). Data predict perturbations in many inter-related pathways, among them MAPK, calcineurin, NMDA receptor, BDNF and serotonin signaling, and adult neurogenesis, plus direct and indirect interactions among several chr 21 proteins. To verify predictions, we compare levels of selected chr 21 and non-chr21 proteins from hippocampus and cortex of the major DS mouse models, chr16 segmental trisomies, Ts65Dn and Ts1Cje, and a new single gene transgenic mouse carrying an extra copy of the chr21 gene, Intersectin (Its1n), a multidomain protein involved in endocytosis and MAP kinase signaling. We examine naive mice and mice that have been stimulated by exposure to behavioral tests or drug treatments. We have identified treatment-dependent abnormalities in the activation levels and/or localizations of critical pathway components, among them, kinases Akt and Erk1/2, transcription factors Elk and CREB, and chr21 proteins, TIAM1 and DYRK1A. Data suggest that the molecular phenotype of DS is characterized by (1) abnormalities in basal levels of protein activities and (2) failures in the dynamics of responses to stimuli. Identifying key points of dysregulation in pathways critical for learning and memory will suggest targets for the testing of potential therapeutics.