DELINEATING EARLY AND LATE EVENTS IN ALZHEIMER’S DISEASE USING SYSTEMS-LEVEL PATHWAY DYNAMICS

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Introduction: Several molecular and cellular pathways notably contribute to the emergence and/or progression of Alzheimer’s disease (AD), and the molecular mechanisms underlying each of these damaged pathways are intensively explored. However, studying the dynamics and putative interactions between these processes involves massive amounts of data and presents a research challenge.

Aims: To separate early and late events in AD, identify globally changed gene families and potential regulatory pathways and discover the underlying molecular mechanisms.

Methods: We use advanced microarrays, and computational system biology approaches to identify dynamic shifts in AD transcript profiles.

Results: Using web-deposited and in-house microarray data we identified several pathways impaired in the AD brain, found dynamic changes between transcript profiles in AD brains from patients with incipient, moderate and severe disease symptoms and those of matched controls and experimentally validated some of these differences. For example, the group of protein folding-related transcripts displayed an early general shift in the cumulative distribution functions of fold changes between AD and control brains, indicating putative involvement of this pathology with the initiation of AD. In comparison, inflammatory response transcripts showed a late general shift, suggesting a consequential role of this pathology in AD progression.

Conclusions: We found distinct disease-related dynamics for new and known AD-related pathways, and characterized their change along disease progression. This data may facilitate the development of effective drug targets by focusing separately on early and later events occurring in the AD brain.