PATHWAY-BASED ANALYSIS OF GENOME-WIDE SIRNA SCREENS REVEALS THE REGULATORY LANDSCAPE OF APP PROCESSING

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Introduction: Ab peptide is produced as a result of proteolytic processing of the amyloid precursor protein (APP). The progressive aggregation of this peptide is a major trait of Alzheimer’s Disease. Processing of APP is complex and is mediated by different enzymes resulting in the production of distinct peptide products. For example, APP can be processed into the non-amyloidogenic peptide sAPP\textsubscript{a}, or the amyloidogenic peptides Ab\textsubscript{40}, Ab\textsubscript{42}, and sAPP\textsubscript{b}. However, to date, the underlying mechanisms that regulate the differential processing of APP remain largely unknown.

Aims: To identify pathways/processes that regulate APP processing.

Methods: We applied a novel pathway-based approach to analyze a large-scale siRNA screen that measures the production of different APP proteolytic products. This method takes into account all genes in a pathway, thus allowing for small effects to be considered, and introduces the concept of scoring ‘pathways’ as opposed to individual genes.

Results: We identified common and distinct pathways that regulate processing of APP into either amyloidogenic peptides or non-amyloidogenic peptides respectively; for example, maturity onset diabetes related pathways differentially regulate the production of sAPP\textsubscript{a} and sAPP\textsubscript{b}. Furthermore, we describe the inter-relationship of these pathways/processes and how they may form cohesive regulatory units of APP processing.

Conclusions: The identification of these processes/pathways, and their relationships to each other, provides, for the first time, a comprehensive systems biology view of the ‘regulatory landscape’ of the APP protein. Such a landscape can provide a framework to explore different therapeutic opportunities that may overcome the limitations of current Ab lowering strategies.