MicroRNA-Based Biomarker in Alzheimer’s Disease

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Alzheimer’s Disease:

- Represents a complex, multifactorial, age- and gender-related, progressive neurogenerative disease
- Heterogenous in presentation and pathophysiology
- Multiple factors contribute to AD symptomatic and molecular-genetic heterogeneity

AD Neuropathology Interrelated Features:

- Progressive disorganization dropout of neocortical synapses → synaptic loss & atrophy
- Neuronal cell death and loss of inter-neuronal communication
- Progressive deposition of amyloid-beta peptides and senile plaques aggregates
- Accumulation of hyperphosphorylated tau protein into neurofibrillary tangles
- Inflammatory neurodegeneration primarily in the association neocortex and hippocampal CA1 region
- Alteration in innate immune response

miRNAs in Alzheimer’s Disease

- miRNAs represent a class of ~19-23 nt single-stranded non-coding RNA that are posttranscriptional regulators of mRNA
- ~2650 individual human miRNAs have been characterized → there are only ~20-35 that are neurologically functional species and highly abundant in CNS
- We found at least 5 proinflammatory miRNAs that are consistently upregulated in AD brain
- These miRNAs were found to downregulate several mRNAs that are involved in the pathophysiology of AD
- The multi-system, multi-pathway, and overlapping regulatory roles for pathogenic miRNAs in CNS make them prime candidates for modulating the expression of many mRNA targets in a progressive and complex disease such as AD
- Downregulation of key and AD relevant mRNAs involved in: phagocytosis deficits and tau pathology (TREM2), inflammation (CFH, IRAK1), and amyloidogenesis (TSPAN12)

miRNAs as Biomarkers

- The highly soluble and mobile miRNAs affect the operation of many of the interactive pathogenic signaling pathways and genetic mechanisms in CNS making them:
  - strategic candidates for promoting AD onset and progression of its pathology
  - Potential indicators for predictive and/or diagnostic biomarkers for AD at any stage

miRNAs for Precision Medicine-Based Diagnostics and Therapeutics

- Many molecular pathways that have been implicated in the pathology of AD are identified in the later stages of the disease
- Identification of the earliest signs of AD and implementing miRNA-based biomarker testing during the prodromal stages of the disease would allow for a better understanding of the molecular pathways involved in AD initiation and trajectory
- Precision medicine-based framework would help understand the heterogeneity of the disease and thus develop better diagnostic and therapeutic methods

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