Circulating Brain-Enriched microRNAs as Biomarkers of Neurodegenerative Diseases

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ISTAART / AABC Webinar on Fluid Biomarkers for AD
May 17, 2017
DiamiR portfolio of biomarkers in development

**Neurodegenerative diseases**
MCI, AD, PD, FTD, ALS, TBI

**Healthy aging**
Monitoring of brain aging

**Neurodevelopmental diseases**
Rett syndrome

**Universal screening test**
Early detection of organ pathology
Abnormal

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/fMRI)
- Tau-mediated neuronal injury (CSF)
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Synaptic dysfunction

Synaptic dysfunction precedes clinical symptoms
>2,000 human miRNAs

miRNAs are short, non-coding, regulatory molecules whose levels change in disease

   based on sequence complementarity a miRNA can bind to and regulate
   >100 mRNAs and a mRNA can be regulated by multiple miRNAs

miRNA sequences are highly conserved across species

miRNAs appear in blood

   secreted / excreted into extracellular space; cross body barriers, incl.
   blood-brain barrier; stable in circulation

Mature technologies are available for miRNA detection

   microarray, NGSeq, qRT-PCR

Certain miRNAs are enriched in specific organs (e.g. brain),
organ regions or tissues (e.g. hippocampus, cortex), cells (e.g. neurons),
cellular compartments (e.g. neurites, synapses)

miRNA-based tests are being used in oncology clinical practice

   (Rosetta Genomics, Interpace Diagnostics)
Hypothesis: ratios of circulating synapse/brain-enriched miRNAs can detect early stages of neurodegeneration

- Pre-selection of miRNAs: enriched in the brain; detectable in plasma; and
  i. present in synapses of brain region(s) known to be affected by disease;
  ii. enriched in other brain regions or cell types
- Quantitative RT-PCR analysis of plasma levels of 35-50 brain-enriched miRNAs
- Algorithm-based selection of effective miRNA biomarker ratios (pairs)
  using pairs of miRNAs increases sensitivity and specificity
- miRNA classifiers (combination of pairs) confirmation in independent cohorts of samples
Two families of brain-enriched miRNAs detect MCI

miR-132 and miR-134 biomarker families

miR-132 family

miR-134 family

MCI: Mild Cognitive Impairment patients; AMC: age-matched control

Sheinerman et al. (2013) Aging, 5:925
Clinically relevant questions

- Detection of MCI / AD in presymptomatic participants
- Prediction of pre-MCI / MCI to AD progression
- Differentiation between neurodegenerative diseases (AD / FTD / PD...)
- Association of miRNA biomarkers with imaging and CSF biomarkers
- Longer term goal: disease and treatment monitoring
CogniMiR™ program status

Assay development
- 24-miRNA classifier
- Protocol optimization, incl. plasma prep tailored to miRNAs
- Potential “feature reduction”
- Analytical validation, SOP
- Clinical validation in multi-site biomarker study in prodromal AD, MCI, AD, control participants

Initial application
- Targeted profiling of brain-enriched miRNA classifiers in plasma
- Clinical Trial Assay (CTA) for patient selection, monitoring of progressors and responders

Source: National Institute on Aging

proprietary
Novel targeted approach to identification of miRNA classifiers of brain and synaptic health in the blood; >1,000 plasma samples analyzed

Brain-enriched miRNAs detectable in plasma as promising and patient friendly biomarkers complementary to other biomarkers

CogniMIR™: clinical assay in development for early AD with initial application in clinical trial support

Research collaborations with pharma, academic and medical centers, disease foundations to analyze multiple independent cohorts

Larger, longitudinal studies are planned

Organ-enriched miRNA technology holds potential for diseases beyond neurodegeneration