Discerning the role of microRNAs in Alzheimer's disease: friends or enemies?

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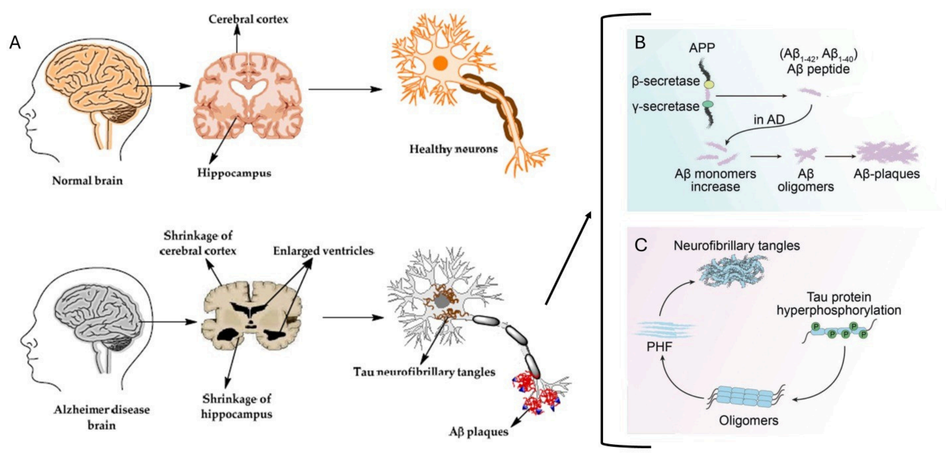
INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and is the primary cause of dementia worldwide. Affected individuals exhibit a marked decline in cognitive functions, leading to impairments in attention, language and daily motor activities. Three AD stages distinguished: pre-symptomatic, prodromal and dementia stage.



AD brain hallmarks

- APP amyloidogenic processing → Neurotoxic Aβ peptides (B)
- Microtubule-associated Tau protein hyperphosphorylation (C)

→ **Aβ plaques + NFTs**

NEURON LOSS

Fig. 1. Healthy brain vs. AD brain. *Modified from: Breijyeh et al. (2020) and Zhang et al. (2024).*

★ MiRNAs: the key players

MicroRNAs (miRNAs) have emerged as specific and promising biomarkers for the early diagnosis of AD.

MiRNAs = short non-coding regulatory transcriptss and are essential gene expression regulators in eukaryotic cells. → **RISC-miRNA complex**

Important target genes!
APP
BACE1
MAPT
Tau kinases

Circulating miRNAs
Circulating miRNAs packaged within exosomes act as intercellular messengers. Their isolation may enable the detection of neuron-derived miRNAs in the circulating fluids of AD patients.

OBJECTIVES

Given the emerging potential of miRNAs, this study aims to...

- Compile information on many differentially expressed miRNAs implicated in AD.
- Examine their effects on AD-related pathological processes.
- Draw some general conclusions regarding their roles and potential applications as biomarkers and/or therapy.

METHODOLOGY

(Alzheimer) OR (AD), (microRNAs) OR (miRNA) OR (miR), ((Alzheimer) OR (AD)) AND ((microRNAs) OR (miRNA) OR (miR)) → PubMed → → R

RESULTS

Parametric analyses: 224 cases

Expression profiles of miRNA across different sources

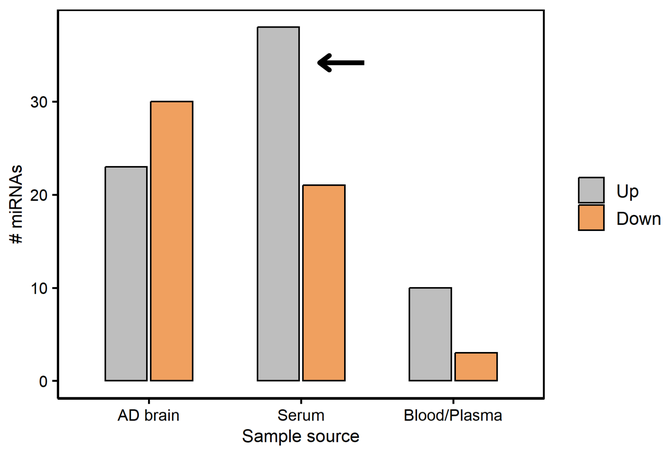


Fig. 2. Number of upregulated and downregulated miRNAs across different sample types.

Expression profiles of miRNA associated with AD pathways

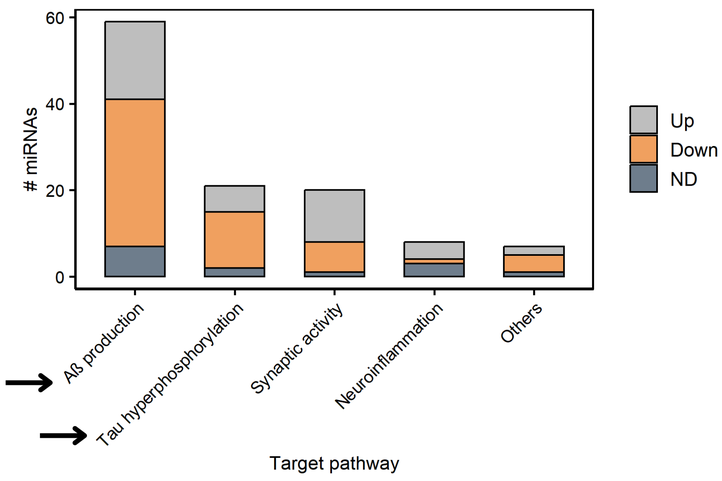


Fig. 3. Number of upregulated and downregulated miRNAs targeting different AD-related pathways. ND: expression not determined.

Expression profiles of miRNA targeting AD genes

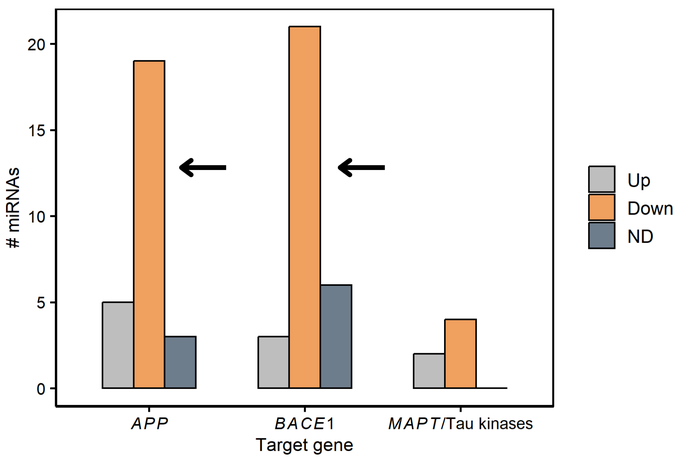


Fig. 4. Number of upregulated and downregulated miRNAs targeting different AD-related genes. ND: expression not determined.

Many miRNAs are dysregulated in serum. Most of the reviewed miRNAs target the *APP* and *BACE1* genes, and are therefore implicated in the Aβ pathway.

DISCUSSION

FRIENDS OR ENEMIES?

It depends on both:
expression levels and target gene/pathway.

Friend — **70%**
Targeting AD genes → Downregulated in AD
Its expression mitigates AD progression

Enemy — **30%**
Targeting functional neuron genes → Upregulated in AD
Its expression enhances AD progression

BIOMARKERS/THERAPY

MiRNAs as biomarkers
The detection of altered expression of miRNAs involved in the development of AD in serum samples, **enables non-invasive diagnosis at very early stages** (when damage is not yet irreversible).

MiRNAs as therapeutic agents
Identifying the target genes or pathways of specific miRNAs is essential for the **development of targeted therapies**. Limitation: complex regulatory network.

CONCLUSIONS

- The **impact of deregulated miRNAs** in AD is associated with their target genes and pathways.
- Most of the miRNAs analysed have been characterised as **friends** (playing a protective role in AD).
- Dysregulated circulating miRNAs may serve as **early biomarkers for AD**.

Future directions
Establishing miRNA panels capable of accurately diagnosing AD.

MAIN REFERENCES

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