Introduction

Alzheimer’s Disease (AD) is the most common type of dementia in the elderly, being a severe neurodegenerative disorder characterized by cognitive impairment and behavioural changes. Pathological hallmarks of AD include synaptic and neuronal loss, astrocytosis, intraneuronal inclusions of hyperphosphorylated tau protein in neurofibrillary tangles (NFT) and extracellular deposits of amyloid (Aβ), also called senile plaques. Aβ is synthesized by β-secretase precursor protein (APP), which can be cleaved by two proteolytic pathways: the non-amyloidogenic pathway and the amyloidogenic pathway (which generates Aβ peptides) (Fig. 1). Disruptions in Aβ clearance and/or production results in their accumulation in brain and blood vessels. There are two main types of AD: early-onset (or familial), which develops before 65 years and is a rare autosomal dominant disease caused by mutations in APP or presenilin genes; and late-onset (or sporadic), that occurs later in life and is a predominant multifactorial and heterogeneous disease.

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. An ideal AD biomarker should:

- Detect fundamental neuropathological hallmarks
- Differ AD from non-AD dementia
- Recognize early stages and distinguish the progression of AD
- Be easy to perform and inexpensive
- Use minimally invasive sample collection
- Be highly reliable, with high levels of sensitivity and specificity

Biomarkers of Alzheimer’s Disease From Peripheral Tissue

Blood-based biomarkers

- Molecular signaling abnormalities arise at early stages
- Easy and minimally invasive collection
- Processing of blood cells is more complex and time-consuming

miRNA as AD biomarkers

miRNAs (microRNAs) are small coding RNAs that act as regulatory modulators of gene expression by two main mechanisms of action (Fig 4):

- Specific miRNAs are expressed in the CNS
- miRNA dysregulation seems to be involved in neurodegenerative processes, such as AD (Table 1)

Challenges of Blood-based biomarkers

- Currently there are no fully validated blood-based biomarkers, owing to:
  - Failure to replicate findings due to high variability between studies
  - Interference with the multiple conditions that affect elderly people

Skin Fibroblast-based biomarkers

- Simple and inexpensive
- Easy to collect from blood without contamination
- It’s possible to repeat experiments
- Detect signal disruptions
- Early diagnosis
- Slow growth in culture
- Biopsy
- Test results

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Conclusions

- The present situation points to a promising future for this field: novel approaches are emerging continuously. The view of AD as a disease not limited to the brain has made easier the detection of potential biomarkers in peripheral tissues such as blood or skin fibroblasts.
- Results obtained until now show a wide range of abnormalities related to AD that would serve as biomarkers of the disease. Nevertheless, in some cases there is controversy between studies and in other cases replication and validation is needed.
- In fact, as none of the individual markers is powerful enough to be applied in routine AD diagnosis, it may be useful to employ combinations of them, in order to achieve high levels of sensitivity and specificity.
- Henceforth it is essential to reach a harmonization of protocols, incorporate methods of validation and start larger studies in order to accomplish a non-invasive AD diagnosis.

Biomarkers Of Alzheimer’s Disease: In Search Of A Non-Invasive Diagnosis

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Materials & Methods

The project has been made as a scientific review using the bibliography obtained from Pubmed Database and Scopus. At first, the search was focused on reviews containing the keywords Alzheimer’s disease, peripheral biomarkers, among others. Then, the information provided by these papers allowed further searches in order to find more specific articles. Papers used have been published mainly between 2010 and 2015 in journals classified in Q1 or Q2.

References