Epigenetics as biomarker for Alzheimer's disease: a new approach to prevention, diagnosis and treatment

Universitat Autònoma de Barcelona

Elena Martínez Ruiz – Biomedical Science Degree – Autonomous University of Barcelona

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder that represents 65-75% of all cases of dementia. Early stages features are typically attributed to age (apathy, lack of attention, loss of motivation…) and advanced stages to impairments for learning and orientation, dyspraxia and anosognosia.

However, the definitive diagnosis is only determined by the presence of β-amyloid plaques (Aβ plaques) and neurofibrillary tangles (NFT) in post-mortem brains.

Familial	Spontaneous
Early-onset (< 65 years old)	Late-onset (> 65 years old)
3% – 5% cases of AD	95% cases of AD
Gene mutations	Genetic and environmental risk factors

TIPS!

Abbreviation	Complete name	Function
DNMT	DNA-methyltransferase	DNA methylation
HMT & HDMT	Histone methyltransferase Histone demethylase	Histone methylation Histone demethylation
HAT & HDAC	Histone acetyltransferase Histone deacetylase	Histone acetylation Histone deacetylation
SAM	S-adenosylmethionine	CH3 donor
APP	Amyloid precursor protein	Membrane protein involved in plaques production
PS1	Presenilin-1	Enzyme for APP cleavage
BACE-1	β-secretase	Enzyme for APP cleavage
NF-KB	Nuclear factor-KB	Neuroinflammation
COX-2	cyclooxygenase-2	Neuroinflammation
NEP	Neprilysin	Enzyme for Aβ degradation
TREM-2	Triggering receptor expressed on myeloid cells-2	Transmembrane receptor
TAU	τ protein	Microtubules stabilization

MATERIALS & METHODS

Data comes from research on PubMed database: scientific literature that includes published reviews and papers.

Selection of literature: by key words, journal and above all publication date (from 2005 to 2015).

Key words: Alzheimer's disease, AD, biomarkers, epigenetics, DNA methylation, histone modifications and non-coding RNA.

Apart from Aβ plaques and NFT, features such as neuroinflammation, gliosis, synaptic dysfunction and cell death can be found in AD patients

RESULTS

Epigenetics regulates genic expression without changing the sequence of DNA nucleotides. Epigenetic signature is **persistent** (as it can be inherited through generations) but also **dynamic** (because it is influenced by environmental stimuli).

Epigenetic changes are involved in phenotypic diversity but also represent a potential risk to develop neurological diseases such as AD.

Three epigenetic mechanisms altered in AD

DNA methylation

Addition of CH_3 to 5' of cytosine forming 5-mC. This process usually occurs in CpG islands, mainly found in the promoter part of some human genes. DNMTs are the enzymes that carry out the reaction using SAM.

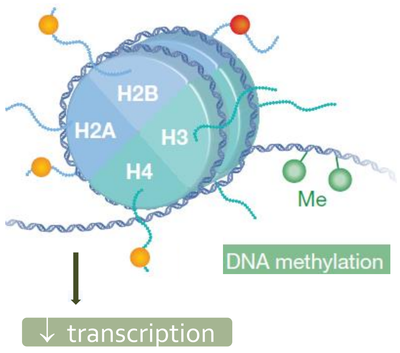
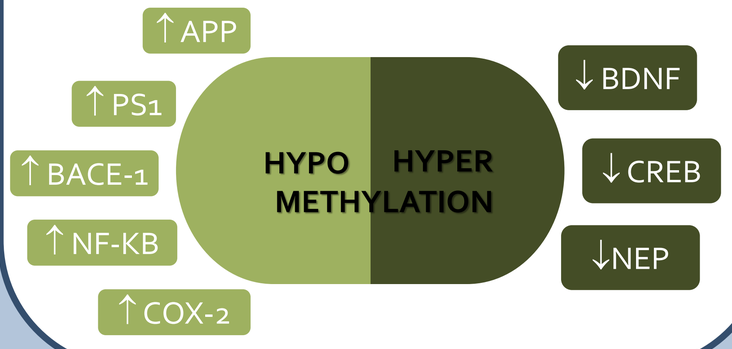


Fig 1. Nucleosome representation, formed by DNA wrapped around a histone octamer. The methylation is indicated in green. DNA methylation leads to reduction of gene transcription.
Adapted from Fischer, 2014

Evidences in post-mortem AD brains and blood samples of patients with clinical dementia that correlates with AD:



Histone tail modifications

Acetylation, methylation, phosphorylation, ubiquitylation, sumoylation and other post-translational histone tail modifications are responsible for the condensation state of chromatin (euchromatin or heterochromatin):

- Histone methylation is regulated by HMTs and HDMTs activity along with SAM accessibility. Its influence on transcription is site-dependent.
- Histone phosphorylation usually favors transcription.
- Histone acetylation is the most studied post-translational modification and it generally increases transcription.

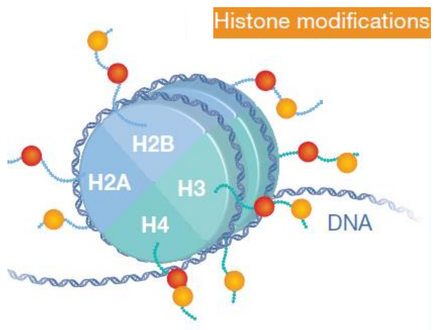


Fig 2. Nucleosome representation. Histone tail modifications are indicated in red and yellow.
Adapted from Fischer, 2014

Evidences in mouse models of AD and cell lines:

- Above all, overactivity of HDAC2 in certain brain areas
  ↳ ↓ transcription

But also…

- Cellular stress → H_3 hyperacetylation → ↑ APP, ↑ PS1, ↑ BACE-1
- Oxidative stress → H_3 hypoacetylation and H_3Lysine9 hypermethylation → ↓NEP

Non-coding RNA: miRNAs

MiRNAs (also known as microRNAs) participate in post-translational regulation of genic expression by RNA silencing. They interfere with mRNA to destabilize it and either provoke its degradation or avoid its translation.

- Each miRNA recognizes up to hundreds of mRNAs.
- Each mRNA is controlled by lots of miRNAs.

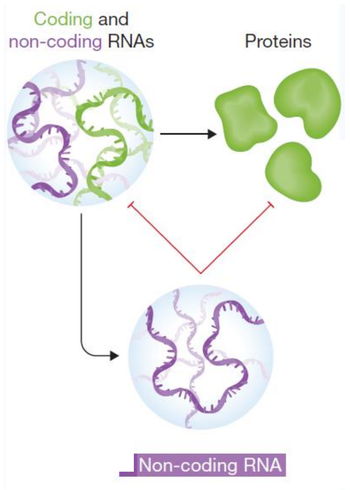


Fig. 3. Non-coding RNAs are indicated in purple. Coding RNAs are indicated in green and they allow the synthesis of proteins.
Adapted from Fischer, 2014

Evidences in post-mortem AD brains and mouse models of AD:

- ↓miR-29 → ↑ BACE-1
- ↑miR-34 → ↓TREM-2
- ↓miR-29 → ↑ TAU

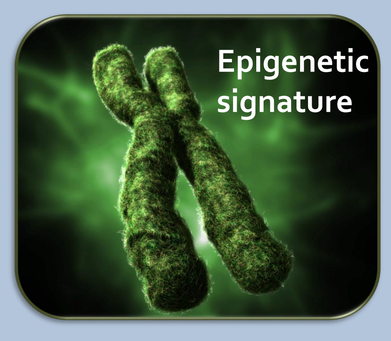
Factors influencing AD development

Life experiences

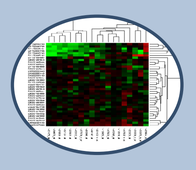
- Physical exercise, consumption of antioxidants…

Risk factors for AD

- **Genetic** → APO-E_4, TREM2…
- **Non-genetic** → age, diet, stress, hypertension, diabetes, smoking, metals, pesticides…



Gene-expression profile linked to memory formation or disease risk



Transmission of disease risk to the next generation?

CONCLUSIONS

- Alzheimer's disease has a big prevalence in global population and no efficient treatment has been found so far.
- Whereas some genetic and environmental factors have been identified to be a risk to the progression of this neurodegenerative disorder, further research is needed to find a way for prevention and early diagnose.
- DNA methylation and histone tail acetylation patterns, as well as miRNAs expression levels have been associated to transcriptional up and down-regulation of certain genes involved in AD development, such as APP, PS1 and BACE-1.
- Research focuses on the identification of biomarkers based on variations of epigenetic mechanisms that can be found in AD patients comparing to same-aged healthy subjects.
- Given that epigenetic alterations could be modified, epigenome studies seem to be a new and promising line for AD therapy.

REFERENCES

The most relevant reviews and articles that helped to prepare this poster are:

1. Coppede F. The potential of epigenetic therapies in neurodegenerative diseases. Frontiers in genetics. 2014;5:220. PubMed PMID: 25071843. Pubmed Central PMCID: 4094885.
2. Fischer A. Epigenetic memory: the Lamarckian brain. The EMBO journal. 2014 May 2;33(9):945-67. PubMed PMID: 24719207. Pubmed Central PMCID: 4193930.
3. Millan MJ. The epigenetic dimension of Alzheimer's disease: causal, consequence, or curiosity? Dialogues in clinical neuroscience. 2014 Sep;16(3):373-93. PubMed PMID: 25364287. Pubmed Central PMCID: 4214179.