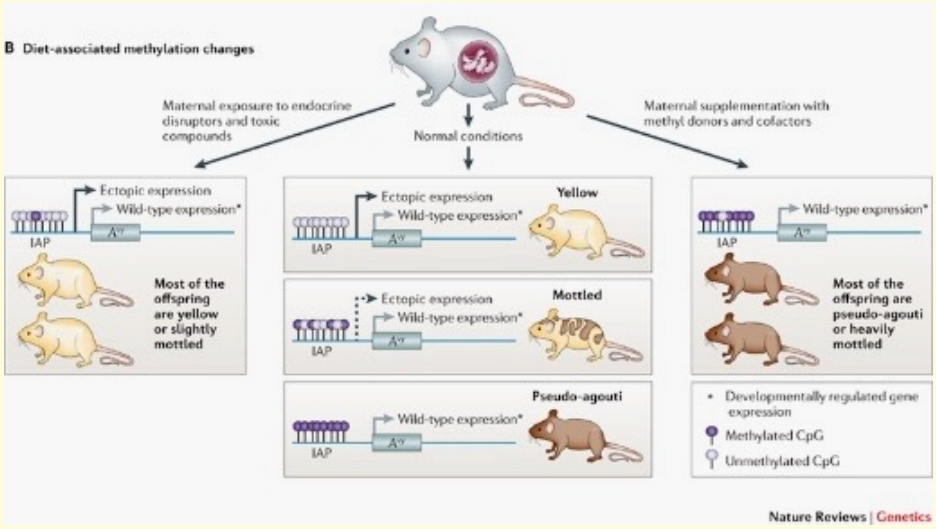
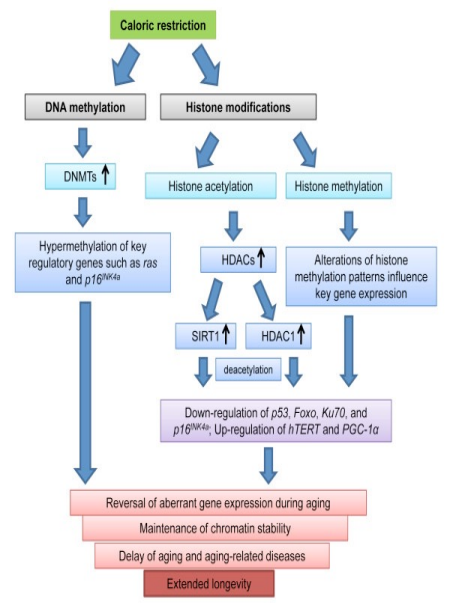
ENVIRONMENT (NUTRITION)

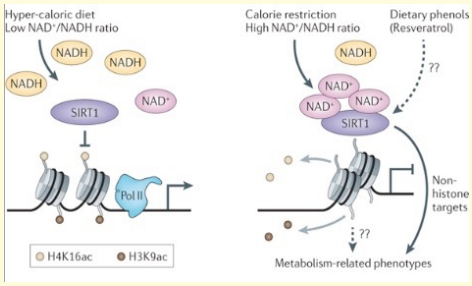
AND EPIGENETICS

The “Agouti mouse” model



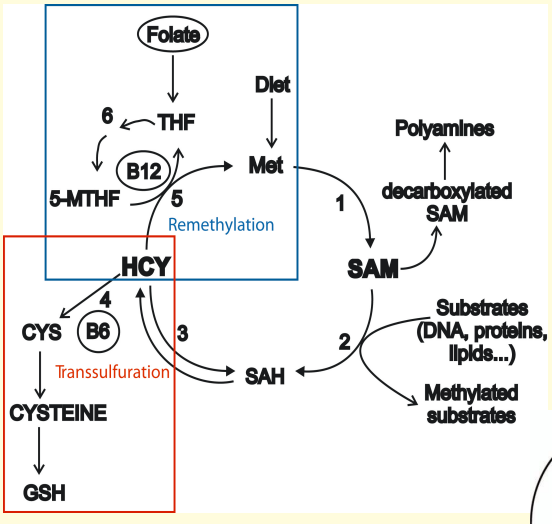
Caloric restriction





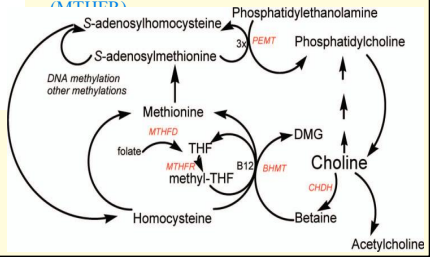
Yuanyuan et al., 2011

One-carbon metabolism

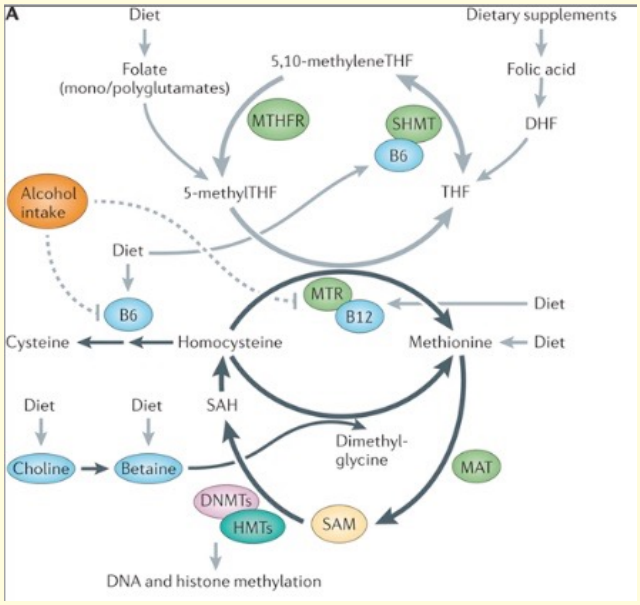


Met, Methionine
SAM, S-adenosylmethionine
SAH, S-adenosylhomocysteine
HCY, Homocysteine
CYS, Cystathionine
GSH, Glutathione
THF, Tetrahydrofolate
MTHF, methyltetrahydrofolate
B12, Vitamin B12
B6, Vitamin B6

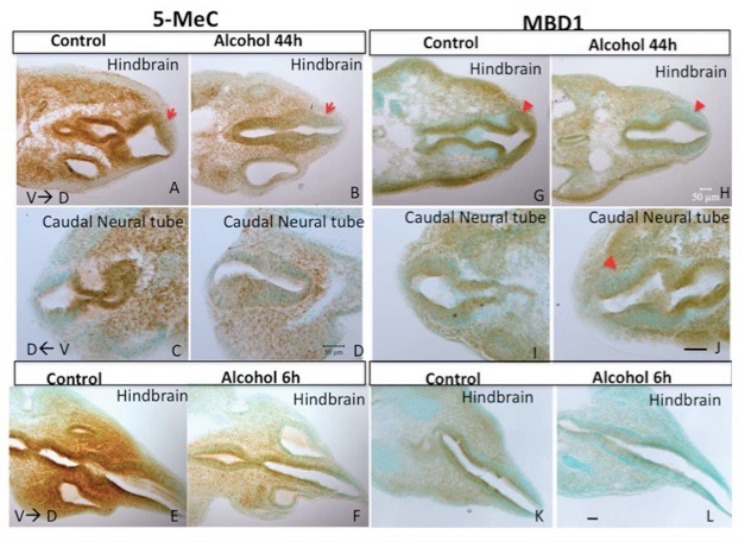
1,Methionine adenosyltransferase (MAT)
2, Methyltransferase(s)
3, SAH hydrolase
4, Cystathionine-β-synthase (CBS)
5, Methionine synthase
6, Methylenetetrahydrofolate reductase



Alcohol and B vitamins



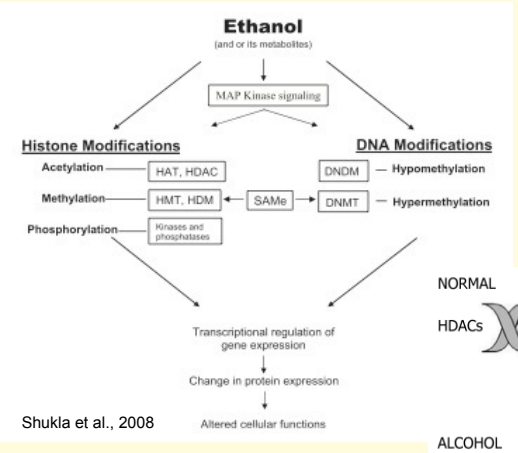
Alcohol consumption and DNA methylation



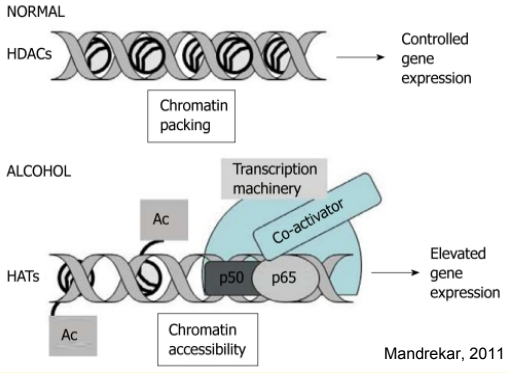
Zhou et al.,, 2011

- Riduzione 5-metilcitosina.
- Ritardo nello sviluppo neurale.

Alcohol and histone acetylation

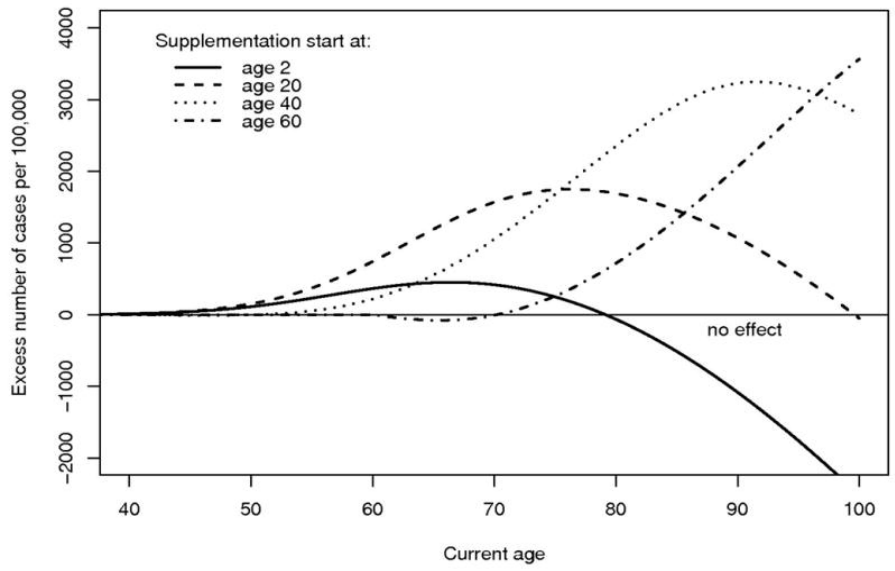


Shukla et al., 2008



Mandrekar, 2011

Folate fortification and colorectal cancer



Metalli

Table 1. An overview of the epigenetic effects of metal exposure

	DNA methylation	Histone modifications	ncRNA expression
Cadmium	√	ND	√
Arsenic	√	√	√
Nickel	√	√	ND
Chromium	√	√[Cr (VI)]	ND
Methylmercury	√	√	ND
Lead	√	ND	ND
Copper	ND	√	ND
Organotin	√	√	ND

√, Reported in the literature; ND, no data (no relevant data was available at the time of this publication).

Cheng et al., 2011

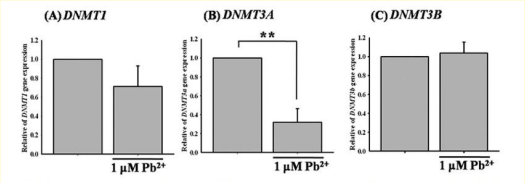
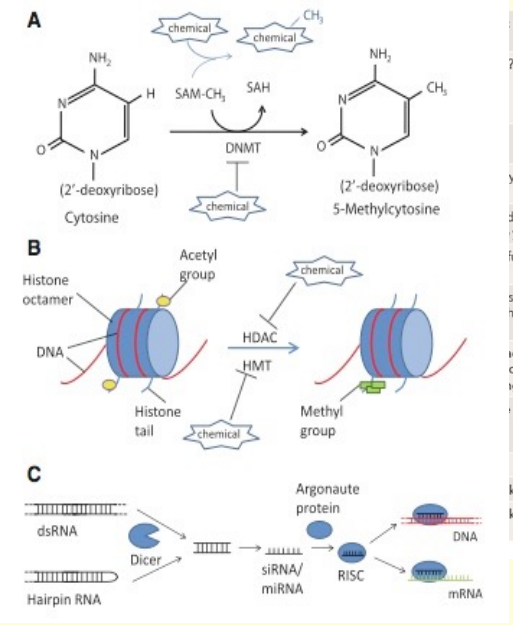


Fig. 2. DNMT gene expression in Pb^{2+}-treated cells. A431 cells were treated with 1 μM $Pb(NO_3)_2$ for 1 h, and total RNA was isolated. Gene expression of *DNMT1* (A), *DNMT3a* (B), and *DNMT3b* (C) were detected by real-time PCR. Values for mRNA levels are means ± SEM. Statistical significance (*$p < 0.05$ and **$p < 0.01$) of the difference between control and Pb^{2+}-treated cells was determined by Student's *t*-test.

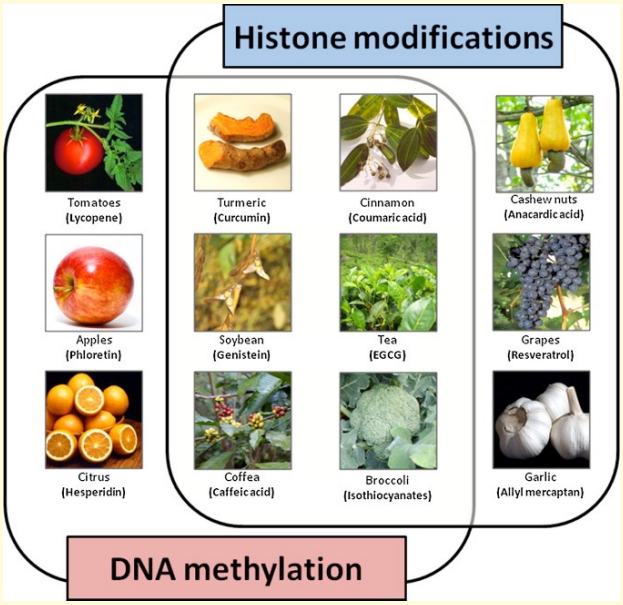
Pollutants and pesticides

Compound		alterations	Refs
Tobacco smoke	H	?	60,61,143
Particulate air pollution	H M		54,69
Asbestos	H	y to different	57
Bisphenol A (BPA)	M	distribution of yellow (A^{vy}) mice	99
Diethylstilbestrol (DES)	M	function	144,145
Metal ions (such as chromium, cadmiun, nickel, arsenic and methylmercury)	M s	sceptibility to as cancer	Reviewed in REFS 146,147
Vinclozolin	M r	d development ogenesis in the g	81,82
Methoxychlor	M	reproductive	84
Silica	H		148
Benzene	H	k of AML	55
Di- and trichloroacetic acid, trichloroethylene	M	k of hepatic	Reviewed in REF. 147

AML, acute myeloid leukaemia



"Epigenetic" vegetables



EPIGENETICS (DNA METHYLATION) AND NEURODEGENERATION

"EPIGENETIC" DISEASES

- **Fragile X Syndrome**
- **Rett Syndrome**
- **ICF Syndrome (Immunodeficiency, Centromeric instability and Facials abnormalities)**
- **Atherosclerosis**

Epigenetics in aging brain

> Different cognitive disorders are associated with epigenetic dysregulation (Graff and Mansuy, 2009)

> DNA methylation in individuals changes over time - hypomethylation (Bjornsson et al., 2008)

> Early-life events may trigger biochemical pathways during aging through epigenetic modifications (Lahiri et al., 2008)

> DNA methylation pattern in human brain seems to be area-specific (Ladd-Acosta et al., 2007)

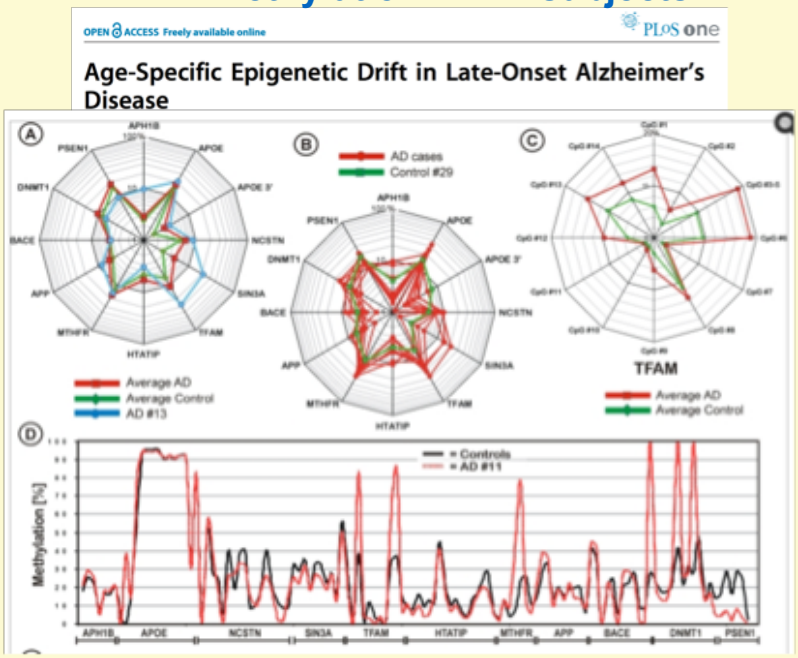
> DNA methylation pattern in human brain is dynamically changing during the lifespan - hypomethylation (Siegmund et al., 2007)

> DNA methylation signatures in development and aging of the human prefrontal cortex (Numata et al., 2012)

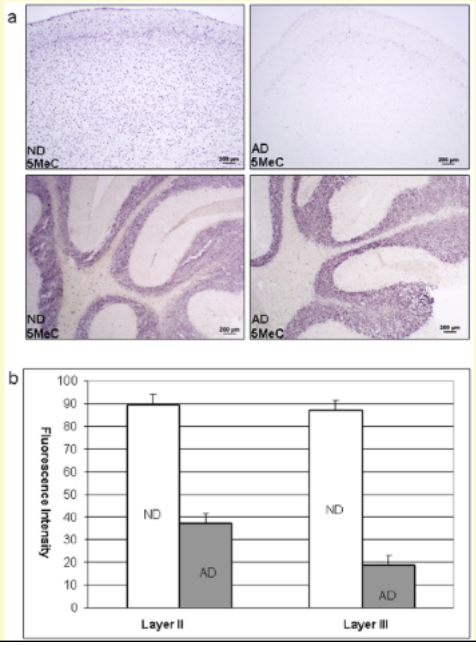
> Longitudinal changes in gene-specific DNA methylation (Madrigano et al., 2012)

> Epigenetic regulation of BDNF affects aging (Zeng et al., 2011)

DNA methylation in AD subjects



Differential DNA methylation in twins discordant for AD



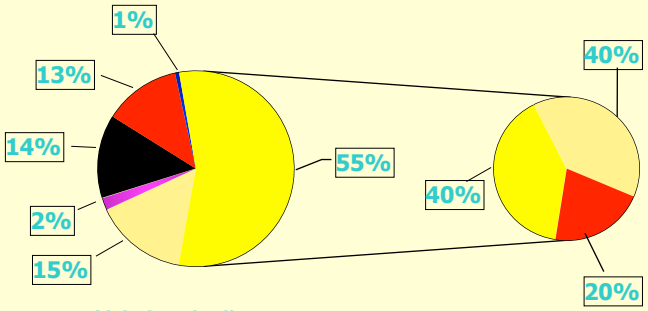
DNMT1, MBD2 and other methylation "markers" are modulated in LOAD patients (Mastroeni et al., 2008)

Alzheimer's Disease (AD)

- Marta, I can't remember the name of that German guy I've lost my mind for...

- Alzheimer, grandma'

Distribution of different forms of dementia



- Alzheimer's disease
- Mild cognitive impairment
- Dementia with Lewy bodies
- Vascular
- Mixed
- Other

- Alzheimer's—mild
- Alzheimer's—moderate
- Alzheimer's—severe

Alzheimer Disease: AD

a progressive CNS disorder with a characteristic pathology

Clinical features:
- memory deficits
- cognitive deficits
- alteration of motor and sensorial functions

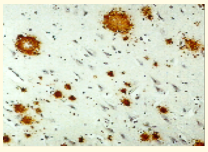
Pathological-anatomical features :
- extracellular deposits of β-amyloid protein (senile plaques)
- Intracellular fibrillar deposits of tau protein (neurofibrillary tangles)
- neuronal death (cortex, hippocampus, amygdala)

Bio-molecular features ?? :
- increased APP expression
- increased β- e γ- secretase activity
- decreased β-amyloid clearance
- increased tau expression
- unbalance of tau phosphorylation/dephosphorylation

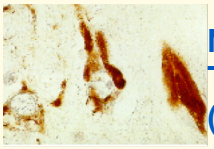
Many possible risk factors: the complex, non-Mendelian disease etiology suggests that an epigenetic component could be involved

Alzheimer's Disease (AD)

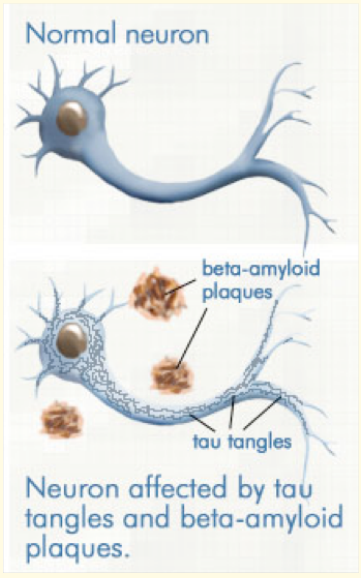
Brain atrophy



Senile Plaques (Amyloid β)

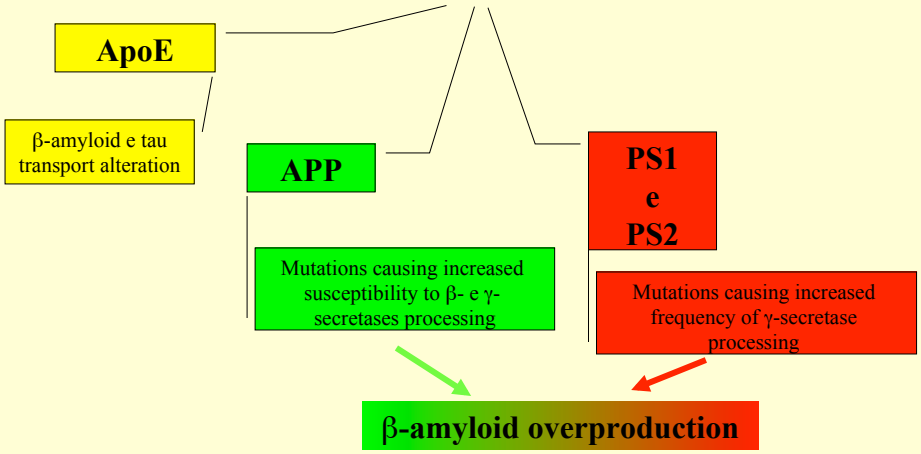


Neurofibrillary Tangles (Tau)



AD: Genetic disease (FAD: familiar AD)

- early onset (40-50 years of age)
- rapid development (2-3 years)
- autosomic dominant genetic pattern
- Due to mutations at specific genes



AD: Sporadic disease (LOAD: Late Onset AD)

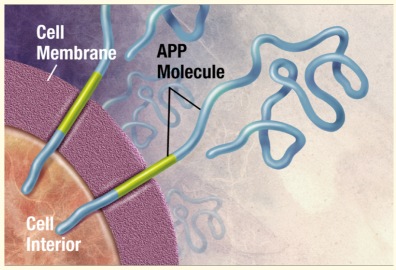
- late onset (after 60 years of age)
- slow development (15-20 years)
- high frequency (over 90% of AD cases)
- many risk factors and possible causes

Possible risk factors in LOAD

- Genetic factors (ApoE)
- Oxidative stress
- Iper-homocysteinemia and B vitamins
- Iper-cholesterolemia
- Cardiovascular diseases
- Lifestyle and education (Brain Reserve)
- Diet and environment

The complex, non-Mendelian disease etiology suggests that an epigenetic component could be involved

PSEN1: the amyloid hypothesis



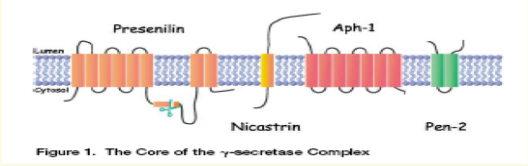
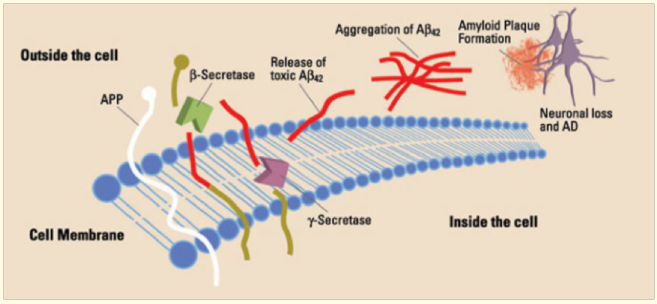


Figure 1. The Core of the γ-secretase Complex

PSEN1 is the main component of the gamma-secretase



NUTRITION, EPIGENETICS AND NEURODEGENERATION

(a paradigmatic example)