# Alzheimer's Disease

Dr. Usman Ghani

Neuropsychiatry Block

# Objectives

Upon completion of this lecture, the students should be able to:

- Define neurodegenerative disorders
- Identify the clinical picture and diagnostic criteria of Alzheimer's disease
- Understand the different ways of processing of amyloid precursor protein leading to amyloid generation and accumulation
- Differentiate between the neuritic plaques, neurofibrillary tangles and tau protein and their role in the pathogenesis of the disease
- Understand the genetics of Alzheimer's disease
- Discuss ongoing research and therapeutic approach to treat these disorders

# Neurodegenerative Diseases



- Diseases of gray matter characterized principally by the progressive loss of neurons

- The pattern of neuronal loss is selective affecting one or more groups of neurons leaving the others intact

- The diseases arise without any clear inciting event in patients without previous neurological deficits

# Neurodegenerative Diseases

- A common theme is the development of protein aggregates that are resistant to normal cellular mechanisms of degradation

- The aggregated proteins are generally cytotoxic

# Alzheimer's Disease

- A degenerative disease with the prominent involvement of the cerebral cortex

- Its principal clinical manifestation is dementia
  - Dementia is the progressive loss of cognitive function independent of the state of attention

- Patients rarely become symptomatic before 50 yr. of age but the incidence of disease rises with age

# Alzheimer's Disease



- The disease becomes apparent with:
  - Gradual impairment of higher intellectual function
  - Alterations in mood and behavior
  - Progressive disorientation
  - Memory loss

- In 5-10 yrs, the patient becomes profoundly disabled, mute and immobile
- Most cases are sporadic
- At least 5-10% are familial

# Diagnosis

- Combination of clinical assessment and radiologic methods

- Pathologic examination of brain tissue is necessary for definitive diagnosis

- Major microscopic abnormalities include: neuritic (or senile) plaques, neurofibrillary tangles and amyloid angiopathy

# Neuritic Plaques
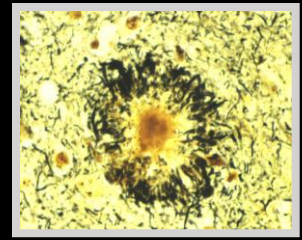


- Spherical with 20-200 µm in diameter
- Contain paired helical filaments as well as synaptic vesicles and abnormal mitochondria
- The amyloid core contains several abnormal proteins
- The dominant component of the plaque core is **Aβ**, a peptide derived from a larger molecule, **amyloid precursor protein** (APP)

# Neuritic Plaques contd..
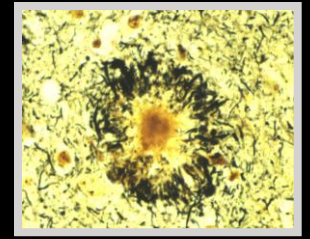


- The two dominant species of Aβ, called **Aβ$_{40}$** and **Aβ$_{42}$** share an N-terminus and differ in length by two amino acids.
- Other less abundant proteins in the plaque:
  - Components of the complement cascade
  - Proinflammatory cytokines
  - $\alpha_1$-Antichymotrypsin
  - Apolipoproteins



Normal    Alzheimer's

Neurofibrillary tangles

Neuron

Amyloid plaques
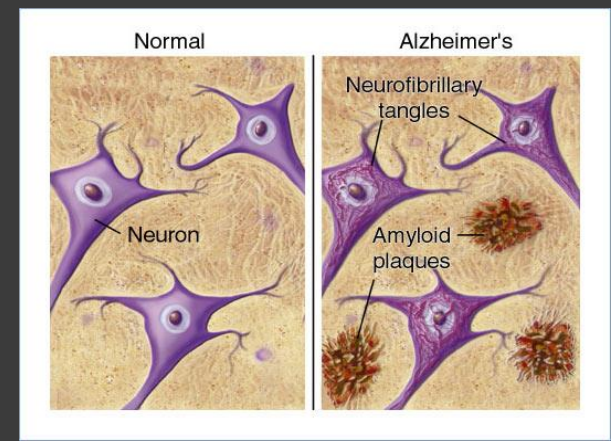
# Neurofibrillary Tangles
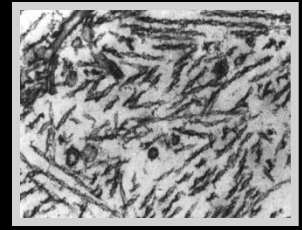
- Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus

- These filaments mainly contain:
  - Hyper-phosphorylated forms of the **tau protein**
  - A protein that enhances microtubule assembly

# Amyloid Angiopathy

- Amyloid proteins build up on the walls of the arteries in the brain

- The condition increases the risk of hemorrhagic, stroke and dementia

- An almost invariable accompaniment of Alzheimer's disease but not specific for Alzheimer's

# Pathogenesis of Alzheimer's



- Still being intensively studied
- Strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques
- Biochemical markers correlated to degree of dementia include:
  - Loss of choline acetyltransferase
  - Synaptophysin immunoreactivity
  - Amyloid burden

# Pathogenesis of Alzheimer's

- Loss of synapses best correlates with severity of dementia

- The Aβ peptide forms β-pleated sheets and aggregates
- Resistant to degradation
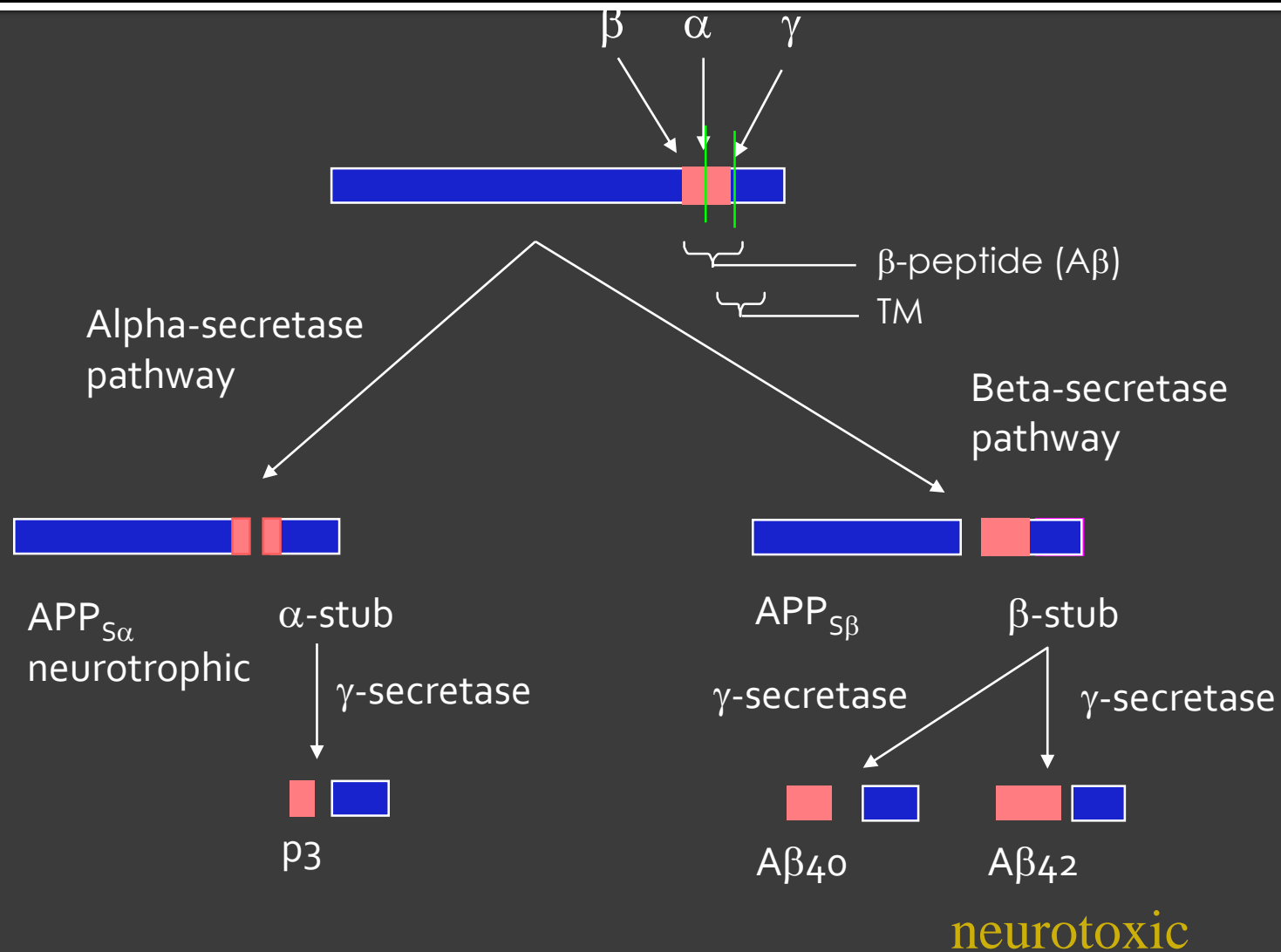- Elicits a response from astrocytes and microglia
- Can be directly neurotoxic

# Aβ is a critical molecule in the pathogenesis of Alzheimer's disease

# Aβ Peptides

- Derived from the processing of APP

- APP is a protein of uncertain cellular function

- It is synthesized with a single transmembrane domain and expressed on the cell surface

# Two pathways for APP processing



β   α   γ

β-peptide (Aβ)

TM

Alpha-secretase pathway

Beta-secretase pathway

$APP_{S\alpha}$ neurotrophic   α-stub

$APP_{S\beta}$   β-stub

γ-secretase

γ-secretase   γ-secretase
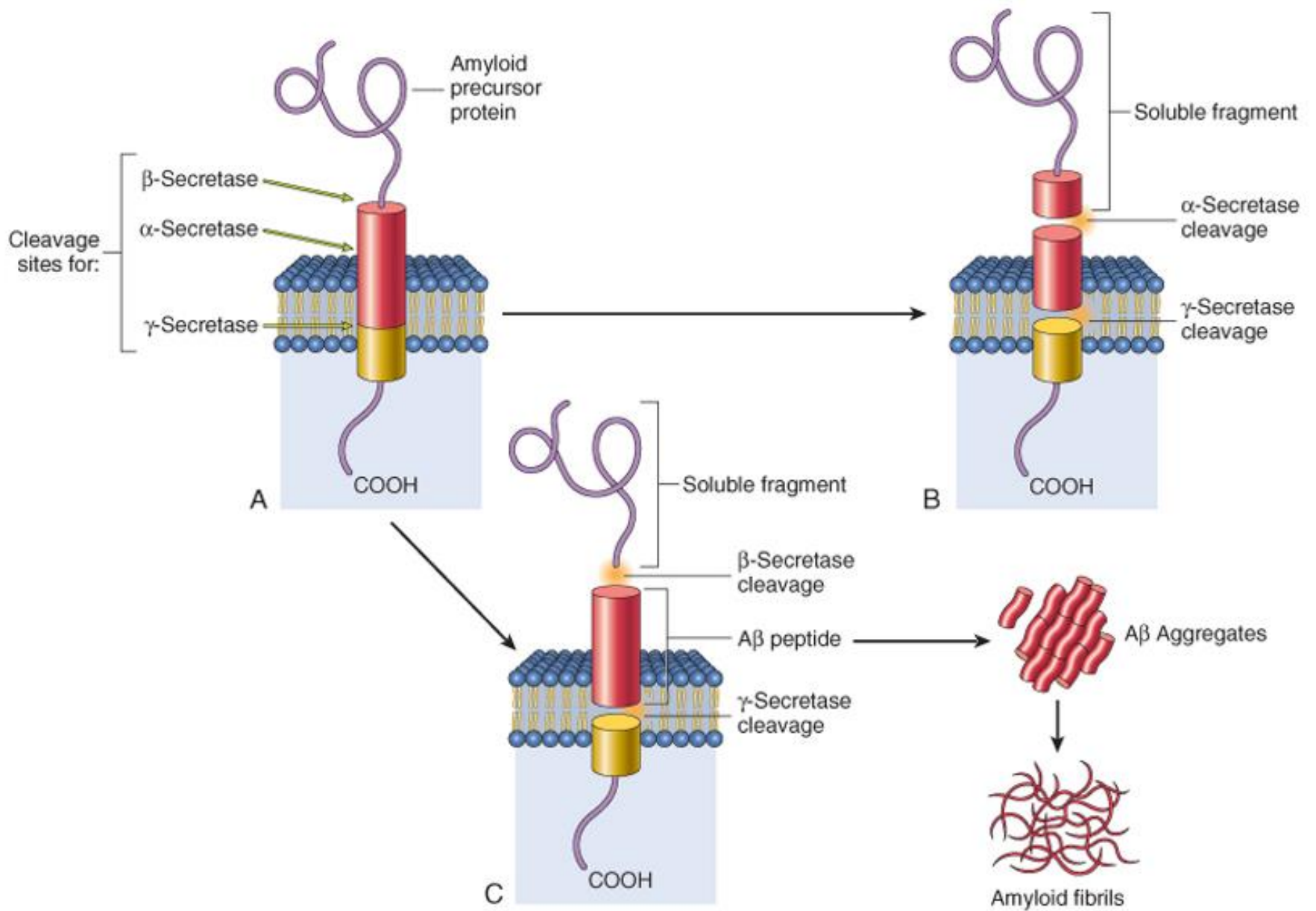
p3

Aβ40   Aβ42

neurotoxic

# Mechanism of amyloid generation

- APP has potential cleavage sites for three distinct enzymes (**α, β, and γ-secretases**)

- The Aβ domain extends from the extracellular side of protein into the transmembrane domain

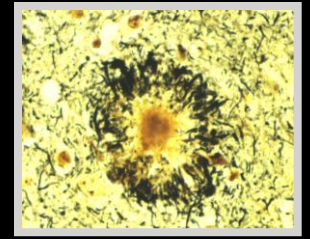- When APP is cleaved by α-secretase, subsequent cleavage by γ-secretase does not yield Aβ

# Mechanism of amyloid generation

- Cleavege by β-secretase followed by γ-secretase results in production of Aβ

- Aβ can then aggregate and form fibrils

Cleavage sites for:
- β-Secretase
- α-Secretase
- γ-Secretase

Amyloid precursor protein

**A**
COOH

**B**
Soluble fragment
α-Secretase cleavage
γ-Secretase cleavage
COOH

**C**
Soluble fragment
β-Secretase cleavage
Aβ peptide
γ-Secretase cleavage
COOH

Aβ Aggregates

Amyloid fibrils

# Accumulation of Aβ protein



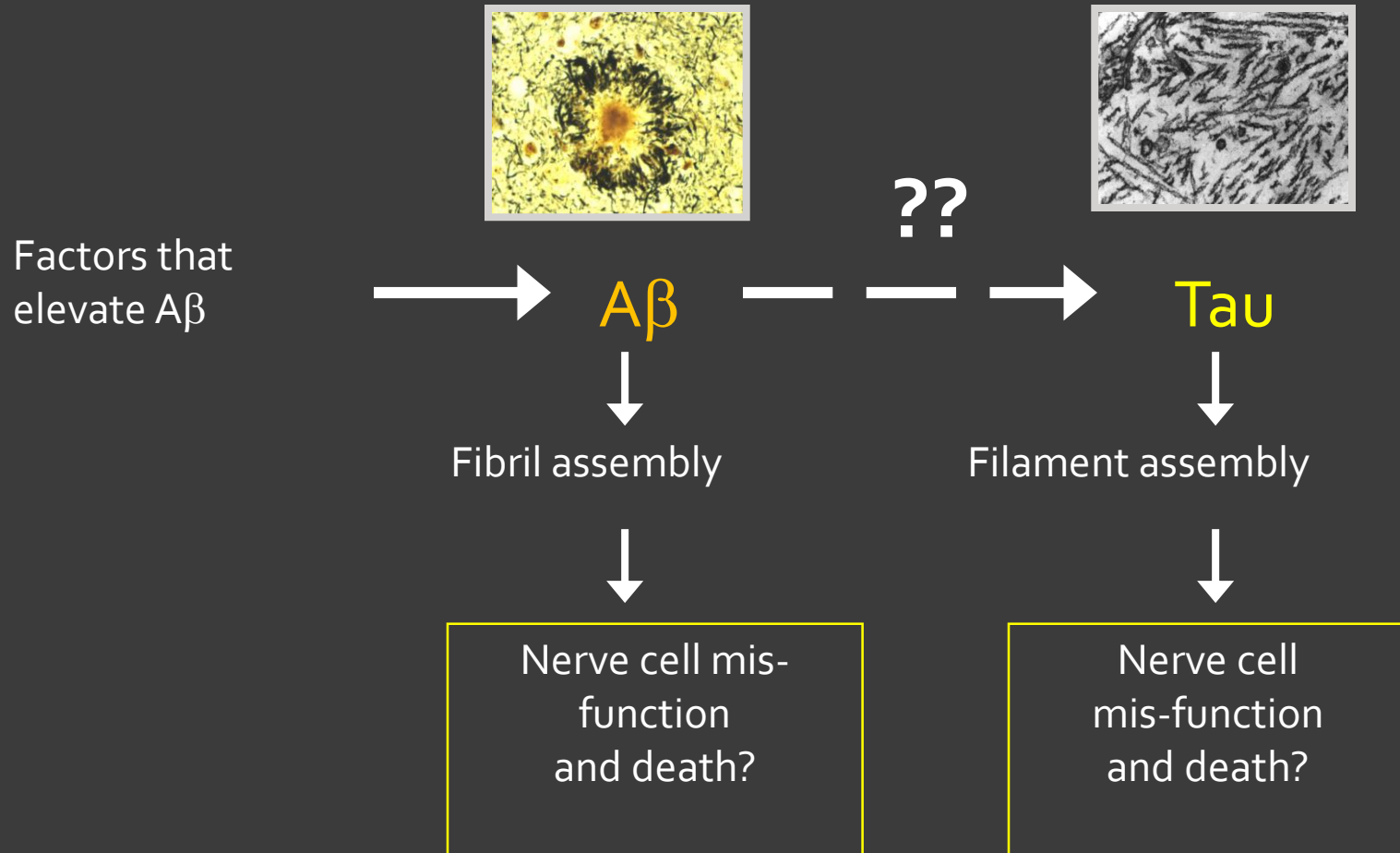- Accumulation of Aβ protein affects neurons and neuronal function:
  - Small aggregates of Aβ alters neurotransmission
  - Aggregates can be toxic to neurons and synaptic endings
  - Larger deposits (plaques) also cause neuronal death
  - Elicit a local inflammatory response leading to further cell injury

# The Tau Protein
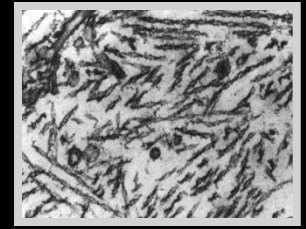
- Presence of Aβ causes hyper-phosphorylation of tau protein in neurons

- This leads to redistribution and aggregation of tau protein into tangles in neurons (from axon into dendrites and cell body)

- The process results in neuronal dysfunction and cell death

# Aβ and Tau may both contribute to the pathogenesis of Alzheimer's Disease



Factors that elevate Aβ → **Aβ** — ?? → **Tau**

Aβ ↓ Fibril assembly ↓ Nerve cell mis-function and death?

Tau ↓ Filament assembly ↓ Nerve cell mis-function and death?

# Genetics of Alzheimer's

- Mutations in APP gene
- Mutations in γ-secretase (presenilin-1 or presenilin-2)
- Both lead to early onset of familial Alzheimer's disease due to high rate of Aβ accumulation

- Alzheimer's occurs in most patients with Down syndrome (trisomy 21) beyond 45 years of age
- The gene encoding APP is located in chromosome 21
- Due to APP gene dosage effects

# Genetics of Alzheimer's

- Genes associated with typical, sporadic Alzheimer's disease are being identified
- This may provide new clues to pathogenesis of the disease

# Genetics of Alzheimer's

| Chromosome | Gene | Consequences |
|---|---|---|
| 21 | Amyloid Precursor Protein (APP) | Early onset FAD Increased Aβ production |
| 14 | Presenilin-1 (PS1) | Early onset FAD Increased Aβ production |
| 1 | Presenilin-2 (PS2) | Early onset FAD Increased Aβ production |
| 19 | Apolipoprotein E (ApoE) | Increased risk for development of AD Decreased age at onset of AD |

# Treatment of AD

- Currently no effective treatment for AD

- Regulating neurotransmitter activity (enhancing cholinergic function improves symptoms)

- Epidemiology shows NSAIDs decrease the risk for developing AD.
- Clinical trials of NSAIDs in AD patients are not very fruitful

# Treatment of AD

- Polyphenols such as flavonoids reduce proinflammatory responses

- Flavonoid supplements may be a new therapeutic approach for AD

# Treatment of AD contd..

Stem cell therapy offers:

- Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration

- Neurotrophic support to remaining cells

- Prevent the production or accumulation of toxic factors that harm neurons

# Continued Research on AD

- The small aggregates of Aβ and larger fibrils are directly neurotoxic

- They can elicit oxidative damage and alterations in calcium homeostasis

- How Aβ is correlated to neurodegeneration in AD? How it is linked to tangles and hyperphosphorylation of tau protein?

- All remain open questions

# Take home message

- Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons
- Extracellular deposition of normally soluble proteins in certain tissues in the form of insoluble fibrous aggregates known as amyloid. The deposition of amyloid interferes with normal cellular function, resulting in cell death and eventual organ failure
- The dominant component of amyloid plaque that accumulates in Alzheimer's disease is amyloid β 42(Aβ42) peptide

# References

- Stem Cell Technology for Neurodegenerative Diseases. Ann Neurol. 2011 September ; 70(3): 353–361.

- A Review: Inflammatory Process in Alzheimer's Disease, Role of Cytokines. The Scientific World Journal, Volume 2012, Article ID 756357,