Amyloid-β Plaques
Contributing To The Pathogenesis Of Alzheimer’s Disease

Zhao Pingping
10051910216
ivyapple@hotmail.com

Neurodegenerative Disease
A condition in which cells of the brain and spinal cord are lost.

- conditions causing problems with movements, such as ataxia
- conditions affecting memory and related to dementia

What belong to neurodegenerative disease
- Alzheimer's disease (AD)
- Parkinson’s disease (PD)
- Huntington’s disease (HD)
- Machado-Joseph disease (Spinocerebellar ataxia type 3)

Brief Introduction
Alzheimer’s disease (AD) is the most common cause of dementia and is a degenerative and terminal disease for which there is currently no known cure.

Early-onset AD
Late-onset AD

Typical symptoms
- Early stages: short-term memory loss
- Later stages: confusion, anger, mood swings, language breakdown, long-term memory loss and the general withdrawal of the sufferer

What’s amyloid-β plaques
Amyloid plaques are mostly made up of a protein called β-amyloid protein which is itself part of a much larger protein called APP (amyloid precursor protein).

Aβ, a 4 kiloDalton peptide, is formed after sequential cleavage of the amyloid precursor protein (APP), a transmembrane glycoprotein of undetermined function.

Fibrillar amyloid accumulation is commonly associated with Dystrophic neurites (神经突起), aberrant sprouting and increased curvature of dendritic processes.

What’s the impact of amyloid accumulation on neuronal circuitry
Step 1
Examine the nature and degree of dendritic abnormalities within and near fibrillar amyloid deposits in fixed brain slices from 4 to 7-month-old transgenic mice over-expressing mutant human amyloid precursor protein and presenilin 1 (PSAPP) (8).

Step 2
To determine the time course over which dendritic and axonal abnormalities occur, by monitoring changes in YFP-labeled dendritic and axonal structures of layer 5 pyramidal cells in living PSAPP/YFPmice. (9)

Step 3
What evidence suggest that the disappearance of neurites between imaging intervals was preceded by gradual development of local structural abnormalities and eventual neurite breakage (11)

Conclusion
The severe neuritic abnormalities, which develop in the vicinity of fibrillar amyloid deposits, eventually lead to disruption and breakage of neuronal branches.

The degree of disruption of neuronal connectivity depends not only on the number of amyloid deposits, but also on their patterns of distribution.

All dendrites passing through fibrillar amyloid deposits showed various degrees of local structural abnormalities of dendritic and axonal abnormalities (Fig1a,b,h) Occur only between 9 and 15μm from the boundary of the fibrillar deposit (Fig1a,d,h) Axons in close proximity to amyloid deposits develop abnormally large varicosities (Fig1f)

In addition to local dendritic spine loss and shaft atrophy fibrillar amyloid deposition also leads to the formation of axonal varicosities within or in the vicinity of deposits (Fig1g,1h).

Many neurites (axons and dendrites) within 15 μm of fibrillar amyloid deposits were gradually eliminated over days to weeks (Fig3a–e,h)

2-4 days: 3.64%
1-2 weeks: 7.6%
4-5 weeks: 36.6%

Neurites in the vicinity of amyloid deposits are progressively eliminated whereas those farther away are stable over time.

1. Neurites within and adjacent to fibrillar amyloid deposits often appeared atrophic with large swellings, indicating substantial disruption of cytoskeletal elements. (Fig1a,b,d)

Time-lapse imaging over days showed these neurites gradually disappearing. (Fig3a–e)

2. A significantly higher percentage of dendrites ended within and in the vicinity of the deposits than farther away. (Fig3f,g,i)

3. An age-dependent reduction in the number of dendrites passing through Aβ deposits.

How is the temporal relation between plaque formation and the changes in local neuritic architecture?

Is plaques a critical mediator of neuritic pathology?
Step 1
Develop a novel technique to explore the formation of amyloid plaques and to determine the effects of newly formed dense-cored plaques on the microarchitecture of the brain. (14)

Step 2
Examine whether the phenotype of plaque formation in as short a period as one week was unique to the aggressive APP/PS1 transgene mouse model (15).

Step 3
Study the interaction between newly formed amyloid plaques and microglia. (17)

Step 4
Study the temporal relation between newly formed plaques and dystrophic neurites. (18)

Fig. 1
Developed a novel in vivo multiphoton imaging technique to recognize newly formed plaques and allows monitoring of their immediate vicinity thereafter to determine the rate of their formation and the temporal sequence of pathophysiological events.

B6C3-YFP mice
5-to-6-month-old

B6C3-YFP mice
5-to-6-month-old

Senile plaque formation is a very rapid event. (Fig. 1d-i)

Newly formed plaques do not change in size after about the first 24h

Image microglia before and after plaque formation

Microglia were attracted to the site of plaque formation within a day (Fig. 2b)

None of the new plaques occurred immediately adjacent to resident microglia.

Microglia do not form the nidus (巢) of new plaques.

Compared the shape and trajectories of yellow fluorescent protein (YFP) fluorescent neurites before and after plaque formation in B6C3-YFP animals.

Neuritic deformation illustrated in individual image slices (Fig. a, c) and in three-dimensional reconstructions (Fig. b, d)
Neurite curvatures were quantitatively analyzed from the in vivo images around each new plaque as well as more than 50μm away from it and compared with control mice. In the immediate vicinity of plaques, the tortuosity increased gradually over the first week, but is indistinguishable from that around all plaques. Neuritic changes occur rapidly and to essentially a maximal extent over first week of a plaque’s presence.

Analyze changes in neurites near plaques on a daily basis

Data suggesting (Step 1, 2, 3, 4)
Dystrophic neurites near amyloid deposits follow amyloid deposition—a period of several days after plaque formation during which progressive cytoskeletal derangements occur in neurites near a plaque.

Amyloid hypothesis
Amyloid deposition
activation and recruitment of microglia
local neuritic changes
Such a sequential cascade leading to neurodegeneration.

Reference

Thank you