Neuroinflammation and microglial activation in Alzheimer’s Disease: in vitro and in vivo models of study.

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Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease, affecting mainly people over the age of 65 and is characterized by cognitive impairments associated with extracellular accumulation of senile plaques composed of beta-amyloid (Aβ) and intracellular deposition of neurofibrillary tangles composed of hyperphosphorylated tau (Tph).

Aβ oligomers (AβO) are the neurotoxic components of the amyloid peptide and are directly involved in the loss of synapses, the neurite network disorganization and the neuronal death. AβO participates in the pro-inflammatory processes, both reactive astrocytes and microglia are colocalized in the vicinity of the Aβ deposits indicating the close link between Aβ and the microglial cells. Microglia, the main immune cells of the brain, have been shown to play key roles in orchestrating this brain inflammation. Reactive glia and associated neuroinflammation are now regarded as playing key roles in both disease initiation and progression. In this work, the close link between microglial cells and the Aβ was investigated.

Methods

IN VITRO EXPERIMENTS

- Rat primary cortical neurons and microglial cells cultured in 96 well-plates (Callizot et al., 2013), in DMEM and serum (4%) (marker of M2 microglial)
- Culture of human microglial cells (HMC3), in 96 well-plates, in EMEM, serum (10 %)
- C57BL6 mice, 18-month old

IN VIVO EXPERIMENTS

- Stereotaxic injections of Aβm (agitated at 37 °C for 3 days)
- 2 μL/side (0.2 μL/min):
  - Lat = ±1.7
  - DV = -1,5; -1,7; -1,9
  - AP = -2,0
- In every systems (primary rat culture, human lines or animal brains) we showed that Aβm induced:
  - strong activation of microglial cells around the lesion, spreading over the time;
  - strong activation of microglial cells and the expression markers of M1 phenotype (A), (B) and cytokine release (C). Phagocytosis of Aβm deposits was also observed (D) after 24 h of contact.

IN VITRO EXPERIMENTS

- Figure 1: Aβm induced neuronal loss and activation of microglial cells in in pro-inflammatory stage resulting in neuronal loss.
- Figure 2: Aβ induced activation of human microglial cells.
- Figure 3: Intra-hippocampal injections of Aβ1-42 induced neuroinflammation in aged mice brain.

Results

- In primary culture of cortical neurons and microglia, Aβm activated microglial cells in a pro-inflammatory stage resulting in neuronal loss.

- Aβ induced large activation of HMC3 cells.

Conclusions

- Whether microglia reaction is beneficial, detrimental or both to AD progression is still unclear, bringing intense debates. This work presented the effects of Aβm/AβO on the microglial activation in different models (cellular and mice).
- In every systems (primary rat culture, human lines or animal brains) we showed that Aβm induced:
  - strong activation of microglial cells around the lesion, spreading over the time;
  - cytokine release (TNFa and IL6).
  - In parallel, phagocytic response to ingest and degrade the insoluble fibrillar Aβ deposits was observed, highlighting the dual and complex role of the microglia in the process of Aβm toxicity.