加齢研セミナー

日　時: 令和元年7月4日(木)午後5時30分～午後6時30分
Thursday, 4 July 2019, 17:30～18:30
場　所: 加齢医学研究所スマートエイジング研究棟2階セミナー室
Seminar Room,Center for Smart Aging Research 2F,IDAC
講　師: 星　美奈子　Hoshi Minako
所　属: 公益財団法人 神戸医療産業都市推進機構 先端医療研究センター
神経変性疾患研究部長　教授
Professor, Department of Brain and Neurodegenerative Disease
Research, Institute of Biomedical Research and Innovation Foundation
for Biomedical Research and Innovation at Kobe
演　題: Na^+, K^+-ATPase α3 is a NEW death target of Alzheimer amyloid-β assembly.
担　当: 瀧　靖之 (スマート・エイジング学際重点研究センター・内線　8582)
Yasuyuki Taki
Co-Deputy Director, Smart-Aging Research Center, Tohoku University
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要　旨: Alzheimer's disease (AD) impairs cognitive function, initially by affecting neuronal synaptic connections and eventually by degeneration of neurons themselves. This brain damage is thought to be caused by a small protein, the amyloid β-protein (Aβ), which becomes neurotoxic by forming varieties of assemblies, collectively referred to "Aβ oligomers." Our laboratory has long been focusing on understanding mechanisms of neurodegeneration in AD and has identified Aβ oligomer from AD patient brains, termed amylospheroids (ASPD), as responsible for neurodegeneration (Hoshi et al. PNAS2003, Noguchi et al. JBC2009). Then, we discovered that the neuron-specific α3 subunit of the Na^+, K^+-ATPase pump (NAKα3), the catalytic subunit that is essential for neuronal excitability, is a toxic target for ASPD (Ohnishi et al. PNAS2015). This is a new system that involves pre-synaptic calcium hyperactivation, which is triggered by impairing NAKα3-derived NAK pump activity, leading to neurodegeneration (Figure 1). Before this finding, NAKα3 had long been considered to be too essential to be the cause of neurodegenerative disease. However, following our finding, the impairment of NAKα3 owing to the binding with misfolded protein assemblies were reported in Parkinson's disease (Shrivastava et al. EMBO J 34, 2408-2423, 2015) and ALS (Ruegsegger et al. Act Neuropathlogy 131, 427-451, 2016). This suggested that the NAKα3 impairment might be a general pathway leading to neurodegenerative diseases. We also discovered that ASPD-binding tetrapeptides blocked the ASPD:NAKα3 interaction and protected mature neurons from ASPD neurotoxicity. Surprisingly, ASPD and α-synuclein share the essential binding region in the fourth extracellular loop of NAKα3. I thus have suggested that a new AD treatment strategy might be based on blocking aberrant ASPD-NAKα3 interaction by masking the ASPD surface with specific peptidomimetics, as shown in figure 2. Recently, we started a collaboration with Dr Chikashi Toyoshima from University of Tokyo who determined the crystal structures of Ca-ATPase and NAKα1. Because ASPD binds the region essential for the rocking motion of the NAKα3 pump, it is reasonable that ASPD binding impairs NAKα3 function. At the seminar, I would be happy to discuss about what we shall do as a next to uncover distribution and function of NAKα3 in health and disease.

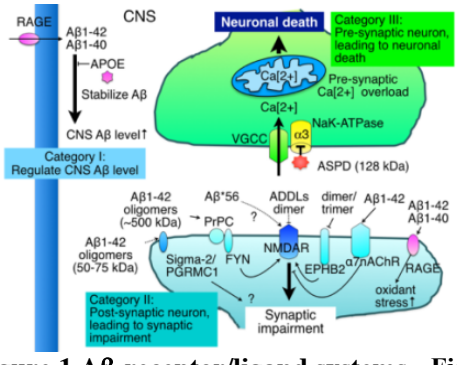

Figure 1.Aβ receptor/ligand systems.

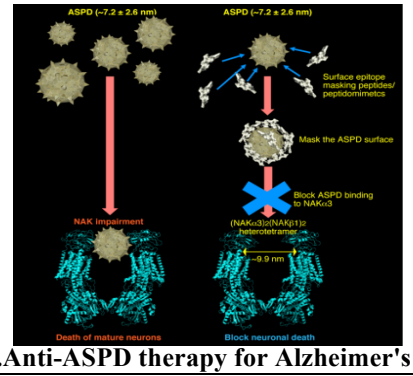

Figure 2.Anti-ASPD therapy for Alzheimer's disease.

主催／加齢医学研究所研究会同窓会