Reconsider Alzheimer’s disease by the ‘calpain-cathepsin hypothesis’

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Abstract

To explain the mechanism of neuronal necrosis after ischemia/reperfusion, the ‘calpain-cathepsin hypothesis’ formulated in 1998 postulates that the post-ischemic calpain activation compromises integrity of the lysosomal membrane, thereby leading to cathepsin spillage. Alzheimer’s disease (AD) is characterized by slowly progressive neuronal death, but its molecular cascade remains elusive for over 100 years. Since accumulation of autophagic vacuoles (granulo-vacuolar degenerations) represents one of the pathologic hallmarks of degenerating neurons in AD, a causative connection between autophagy failure and neuronal death should be present.

Here, the author provides a comprehensive overview of key findings suggesting that ischemic neuronal death and Alzheimer neuronal death may share a common molecular cascade. Recent data advocate for dual roles of heat shock protein 70.1 (Hsp70.1) as a molecular chaperone for damaged proteins and a guardian of lysosomal integrity. Lysosomal rupture is caused by autophagy failure due to activation of calpains, generation of 4-hydroxy-2-nonenal (HNE) that carbonylates Hsp70.1, and calpain-mediated cleavage of carbonylated Hsp70.1. The author discusses three topics; (1) how age-related decrease in lysosomal and autophagic activities has a causal connection to programmed neuronal necrosis, (2) how genetic factors such as apolipoprotein E and presenilin 1 can facilitate lysosomal destabilization in the sequential molecular events, and (3) whether a single cascade can simultaneously account for implications of all players previously reported.

In conclusion, Alzheimer neuronal death conceivably occurs by the similar ‘calpain-hydroxynonenal-Hsp70.1-cathepsin cascade’ with ischemic neuronal death. Blockade of calpain or extra-lysosomal cathepsins as well as scavenging of HNE could be an effective AD therapeutic approach.

Biography

Dr. Yamashima graduated from Kanazawa University School of Medicine in 1975, and completed his Ph.D in 1979. He is now a director of Restorative Neurosurgery and Neuroscience, participating in both basic research using macaque monkeys and clinical practice in Psychology in Kanazawa University Hospital. He has published more than 200 papers in reputed journals and his main subjects are ‘neuronal death’ and ‘adult neurogenesis’, specific for the primates. Last year, he published a book entitled ‘Vegetable oils will kill your brain (in Japanese)’, alarming risks of linoleic acid-derived HNE involved in the cooking oils as a cause of Alzheimer disease.