細胞生物学セミナー

Endosomal-Lysosomal Dysfunction as a Primary Catalyst for Alzheimer's Disease

Ralph A. Nixon[1, 2,3,4] and Ju-Hyun Lee[1, 2]

[1]Center for Dementia Research, Nathan S. Kline Institute, Orangeburg, NY 10962 USA; Departments of [2]Psychiatry, [3]Cell Biology; [4] NYU Neuroscience Institute, New York University Langone Health, New York, NY 10016 USA.

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In Alzheimer's Disease (AD), autophagy is induced in vulnerable neurons as an early neuroprotective response but is soon countered by progressive decline of lysosomal proteolysis leading to extreme autophagic stress and diverse pathological consequences. In human familial-AD cells and mouse models of AD, mutations of genes causing monogenic AD (*PSEN1, APP*), or late-onset AD (e.g. *APOE4*) are now implicated directly via multiple mechanisms disrupting vATPase and acidification of lysosomes, thereby setting off a cascade of additional pathogenic events. The ethio-pathogenic importance of deficient lysosomal acidification on autophagy and the consequent neurodegenerative cascade in these models is underscored by rescue effects achieved by correcting lysosomal pH. The pathogenic cascade triggered by early autophagy/lysosome failure was recently revealed by multi-dimensional analysis of five different AD mouse models in which *in vivo* autophagy was interrogated using a transgenic mRFP-eGFP-tagged LC3 probe expressed selectively in neurons and an array of correlative confocal and ultrastructural approaches. Ratiometric pH analysis revealed appearance of poorly acidified enlarged autolysosomes (AL), in which APP-βCTF and Aβ selectively accumulated well before amyloid deposits extracellularly. Rare in normal perikarya, these de-acidified ALs accumulated massively in the most compromised perikarya, packing into huge projecting membrane blebs and coalescing with endoplasmic reticulum networks that yielded intra-lumenal fibrillar β-amyloid. β-amyloid within still intact perikarya assumed the appearance of amyloid-plaques and, indeed, eventual cell death quantitatively transformed them into the primary source of extracellular plaques. These results showing that β-amyloid-plaques originate from dying neurons rather than the reverse as conventionally hypothesized, has novel therapeutic implications.
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Keywords: Alzheimer's disease, Amyloid Precursor Protein, v-ATPase, lysosome acidification, autophagy

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【後援】　基礎研究医養成プログラム、順天堂大学大学院医学研究科
【問い合わせ先】　老人性疾患病態・治療研究センター　内山安男 (内 3798)
老人性疾患病態・治療研究センター　谷田以誠 (内 3601)
器官・細胞生理学講座　小松雅明 (内 3512)