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Study of Exosomes Shed New Light on Physiology of Amyloidogenesis.

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Abstract

Accumulation of toxic amyloid oligomers, a key feature in the pathogenesis of amyloid-related diseases, results from an imbalance between generation and clearance of amyloidogenic proteins. Cell biology has brought to light the key roles of multivesicular endosomes (MVEs) and their intraluminal vesicles (ILVs), which can be secreted as exosomes, in amyloid generation and clearance. To better understand these roles, we have investigated a relevant physiological model of amyloid formation in pigment cells. These cells have tuned their endosomes to optimize the formation of functional amyloid fibrils from the premelanosome protein (PMEL) and to avoid potential accumulation of toxic species. The functional amyloids derived from PMEL reveal striking analogies with the generation of Aβ peptides. We have recently strengthened these analogies using extracellular vesicles as reporters of the endosomal processes that regulate PMEL melanogenesis. We have shown that in pigmented cells, apolipoprotein E (ApoE) is associated with ILVs and exosomes, and regulates the formation of PMEL amyloid fibrils in endosomes. This process secures the generation of amyloid fibrils by exploiting ILVs as amyloid-nucleating platforms. This physiological model of amyloidogenesis could shed new light on the roles of MVEs and exosomes in conditions with pathological amyloid metabolism, such as Alzheimer's disease.

KEYWORDS:

Alzheimer; Amyloid; ApoE; Aβ; Endosomes; Exosomes; Intraluminal vesicles; MVB; PMEL; Pigmented cells

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