

PIKfyve complex regulates early melanosome homeostasis required for physiological amyloid formation

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Abstract

The metabolism of PI(3,5)P₂ is regulated by the PIKfyve, VAC14 and FIG4 complex, whose mutations are associated with hypopigmentation in mice. These pigmentation defects indicate a key but yet unexplored physiological relevance of this complex in the biogenesis of melanosomes. Here we show that PIKfyve activity regulates formation of amyloid matrix composed of PMEL protein within early endosomes, called stage I melanosomes. PIKfyve activity controls the membrane remodeling of stage I melanosomes that increases PMEL abundance and impairs its sorting and processing. PIKfyve activity also affects stage I melanosome kiss-and-run interactions with lysosomes that is required for PMEL amyloidogenesis and establishment of melanosome identity. Mechanistically, PIKfyve activity promotes the formation and membrane tubules from stage I melanosomes and their release by modulating endosomal actin branching. Together our data indicate that PIKfyve activity is a key regulator of the melanosomal import-export machinery that fine tunes the formation of functional amyloid fibrils in melanosomes and the maintenance of melanosome identity.

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