Mechanism of amyloid formation during melanosome biogenesis

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Research Abstract

? DESCRIPTION (provided by applicant): PMEL is a key factor in melanocytes and operates in the pigmentation pathway that protects our skin from skin cancer. To this end, the protein forms a physiological amyloid matrix in melanosomes. This matrix serves for the deposition of the pigment melanin, which shields our skin against hazardous UV irradiation. PMEL was the first physiological amyloid to be discovered in human cells. It is a cousin of the more (in) famous pathological, toxic amyloids linked with various incurable diseases, such as Alzheimer's and

Parkinson’s Disease, prion diseases, diabetes, and cancer. However, physiological amyloids like PMEL share various aspects and certain pathways of formation with their pathological counterparts and some assemble and/or accumulate in similar endocytic compartments. Thus, PMEL is an attractive model system to study amyloids and additionally holds the promise of revealing fundamental secrets of melanocyte and pigmentation biology. While PMEL behaves like a conventional membrane protein in early secretory compartments, it unleashes a massive potential for aggregation once it arrives in the melanosome. We aim to examine how the molecule senses the specific melanosomal environment, to characterize the structural transitions of the molecule in response to this environment, and to investigate how the process is regulated. Additionally, we seek to understand how PMEL manages to assemble into amyloid without developing the toxicity for which amyloids are notorious. Finally, we propose to characterize the molecular and cellular requirements for PMEL amyloid formation focusing on the role of Rab GTPases and their effectors in the process. In the context of our preliminary results, we already identified one particular Rab GTPase whose function appears to be required for proper PMEL processing and we will investigate how it works. Our search for cellular factors promoting amyloid formation may discover key molecules involved in establishing the identity of early melanosomes, the organelles that provide the optimal environment for PMEL to form fibrous amyloid. Our specific aims are (1) Characterizing how the functional interplay of the PMEL domains drives amyloid formation and (2) Identifying molecular & cellular requirements for amyloid formation.

Further information available at:

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