Functional Amyloid in Melansome Biogenesis

https://neurodegenerationresearch.eu/survey/functional-amyloid-in-melansome-biogenesis/

Principal Investigators

MARKS, MICHAEL S

Institution

CHILDREN'S HOSP OF PHILADELPHIA

Contact information of lead PI
Country

USA

Title of project or programme

Functional Amyloid in Melansome Biogenesis

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,622,018.35

Start date of award

01/09/2001

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

amyloid formation, Pigments, Melanosomes, Amyloid, Biogenesis

Research Abstract

DESCRIPTION (provided by applicant): Melanosomes are subcellular organelles in which melanin pigments are synthesized and stored within skin melanocytes and pigment cells of the eye. Within melanosomes, newly synthesized melanins polymerize on a sheet-like matrix of proteinaceous fibers that are largely composed of a single protein, PMEL. PMEL fibrils have biophysical features of amyloids like those associated with neurodegeneration in Alzheimer and

Parkinson Diseases, but PMEL fibrils are non-pathogenic and serve a physiological role in pigmentation. By assessing how PMEL fibrils form within melanosome precursors and how their formation differs from that of pathogenic amyloid fibrils, we may better understand how to divert pathological amyloid into non-pathological forms. This proposal aims to (1) define molecular mechanisms that regulate physiological PMEL amyloid formation, and (2) test whether mutations that alter PMEL amyloid properties confer toxicity. Whereas pathological amyloids form slowly in solution, in vitro PMEL rapidly polymerizes into amyloid upon dilution out of denaturant, suggesting that the rate of fibril formation might be critical to distinguish functiona from pathological amyloid. How fibril formation is regulated in vivo is not known. Our preliminary data show that mature forms of PMEL just prior to fibril formation are disulfide bonded to a protein that we are in the midst of identifying. Mutations that interfere with this association hav no effect on early PMEL folding, processing or trafficking to endosomal compartments, but ablate the ability of PMEL to polymerize into amyloid fibrils in cells. This association thus likel impacts conformational changes required for amyloid formation. Preliminary data also show that fibrils begin to form in endosomes in association with intralumenal membrane vesicles (ILVs), suggesting that the ILVs themselves participate in amyloid biogenesis. Here, we will test the role of each of these factors in PMEL amyloid formation, and thereby begin to define the molecular mechanisms underlying the conformational change that converts PMEL from a soluble protein into physiological amyloid. Mice that lack a functional Pmel gene generate melanosomes without fibrils but have only modest defects in skin pigmentation. By contrast, several animal models bearing PMEL orthologues with dominant mutations are severely hypopigmented; human PMEL mutants bearing these mutations generate fibrils that have distinct morphological and functional properties and that inhibit melanogenesis in cultured cells. We hypothesize that the mutations render functional PMEL amyloid toxic to melanocytes. We will test this hypothesis in Aim 3 by expressing the mutant PMEL forms in mice and assessing their effect on pigment cell viability. Our Specific Aims are: 1. To determine how a disulfide bonded associated protein facilitates PMEL amyloid formation; 2. To test whether PMEL amyloid formation is seeded by endosomal membranes; and 3. To test whether dominant mutations in PMEL generate toxic amyloid in pigment cells.

Lay Summary

PUBLIC HEALTH RELEVANCE: Within melanosomes – subcellular organelles of pigment cells of the eye and skin – melanin pigments deposit on fibrils that resemble amyloid, a protein fold normally associated with neurodegeneration (as in Alzheimer and Parkinson Diseases). However, the melanosome fibrils are functional and not pathological. The goal of this proposal is to understand how functional PMEL amyloid forms and whether genetic alterations in its formation generate toxic amyloid. If successful, our results might explain novel forms of pigment loss and lead to novel approaches to detoxify pathological amyloid formation in neurodegenerative diseases and other amyloidoses.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A