Chaperone-Assisted Assembly of Membrane Trafficking Complexes

Jingshi Shen

Department of Molecular, Cellular and Developmental Biology, University of Colorado, US

Email: jingshi.shen@colorado.edu

Vesicle-mediated cargo transport relies on multimeric trafficking complexes such as adaptor protein complexes to capture cargo and drive vesicle budding and fusion [1, 2]. Our previous studies of adaptor protein complexes suggest that faithful assembly of a trafficking complex in the cell depends on dedicated assembly chaperones [3-5]. In a genome-scale CRISPR screen, we identified alpha and gamma adaptin binding protein (AAGAB, also known as p34) as a chaperone essential to the assembly of AP2, a heterotetrameric adaptor protein complex regulating clathrin-mediated endocytosis (CME) [5]. AAGAB assists AP2 assembly by sequentially binding and stabilizing the alpha and sigma subunits of AP2. Without the assistance of AAGAB, AP2 fails to assemble, leading to degradation of AP2 subunits and disruption of CME. In humans, heterozygous AAGAB mutations cause punctate palmoplantar keratoderma type 1 (PPKP1), a skin disorder, and are linked to increased incidents of cancer [6-8]. In my talk, I will present our unpublished findings of how AAGAB recognizes AP2 subunits and facilitates their assembly into heterotetrameric complexes. I will also discuss our searches for additional chaperones acting in concert with AAGAB to control the assembly of AP2 and other adaptor protein complexes.

References:

1. Dell'Angelica, E.C. and J.S. Bonifacino, *Coatopathies: Genetic Disorders of Protein Coats.* Annu Rev Cell Dev Biol, 2019. **35**: p. 131-168.
2. Yu, H. and J. Shen, *Faithful SM proteins chaperone SNAREs on path to successful assembly.* Proc Natl Acad Sci U S A, 2023. **120**(3): p. e2219769120.
3. Tian, Y., et al., *Oligomer-to-monomer transition underlies the chaperone function of AAGAB in AP1/AP2 assembly.* Proc Natl Acad Sci U S A, 2023. **120**(2): p. e2205199120.
4. Wan, C., et al., *AAGAB is an assembly chaperone regulating AP1 and AP2 clathrin adaptors.* Journal of Cell Science, 2021. **134**(19).
5. Gulbranson, D.R., et al., *AAGAB Controls AP2 Adaptor Assembly in Clathrin-Mediated Endocytosis.* Dev Cell, 2019. **50**(4): p. 436-446 e5.
6. Nomura, T., et al., *Punctate Palmoplantar Keratoderma Type 1: A Novel AAGAB Mutation and Efficacy of Etretinate.* Acta Dermato-Venereologica, 2015. **95**(1): p. 110-111.
7. Pohler, E., et al., *Haploinsufficiency for AAGAB causes clinically heterogeneous forms of punctate palmoplantar keratoderma.* Nat Genet, 2012. **44**(11): p. 1272-6.
8. Elhaji, Y., et al., *AAGAB Mutations in 18 Canadian Families With Punctate Palmoplantar Keratoderma and a Possible Link to Cancer.* J Cutan Med Surg, 2020. **24**(1): p. 28-32.