How is the membrane protein folded?

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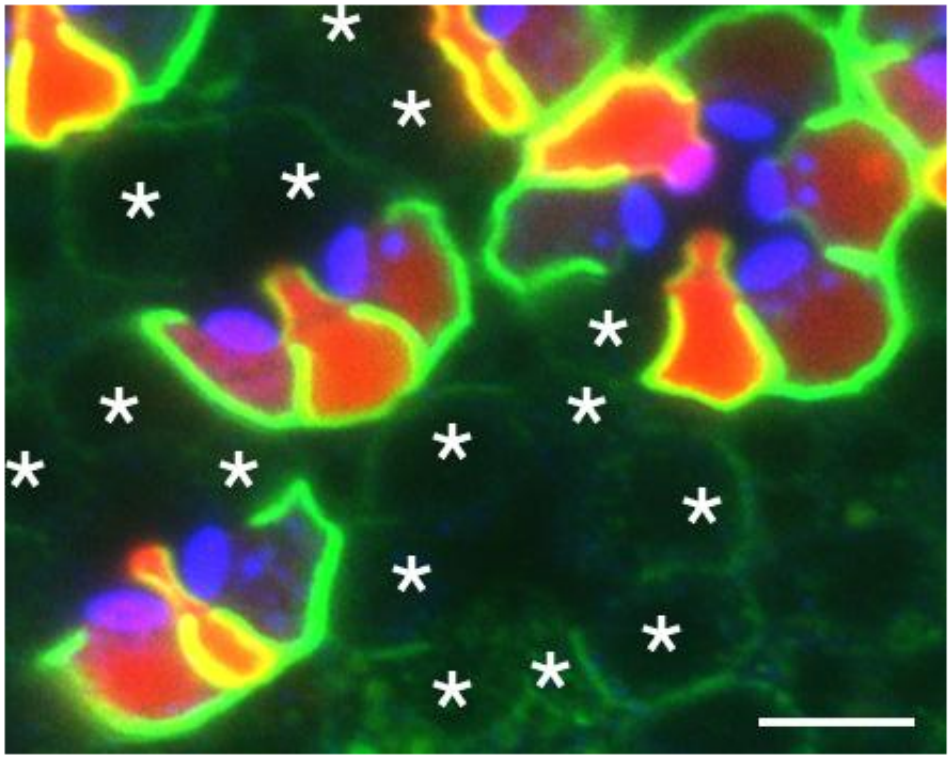

Immunostaining of a dPob-deficient Drosophila mosaic retina expressing red fluorescent protein as a wild-type cell marker (red), by using anti-rhodopsin antibody (blue) and anti-Na+K+ATPase (green). The asterisks (*) show dPob-deficient homozygous photoreceptors. dPob-deficient photoreceptors lack all multi-pass proteins, but not the membrane proteins that Dr. Satoh investigated. Credit: Division of Life Science, Graduate School of Integral Arts and Science, Hiroshima University

A key factor in the biosynthesis and stable expression of multi-pass

transmembrane proteins was discovered, and its loss is thought to cause retinal degeneration. The factor works especially for multi-pass membrane proteins, in the integration of polypeptides into the membrane and/or protein folding. Understanding the mechanisms underlying protein folding and trafficking may contribute to the large-scale, therapy-based production of target proteins.

In 2013, the Nobel Prize in Physiology or Medicine was awarded to Randy W. Schekman, James E. Rothman, and Thomas C. Südhof for their discovery of how cells deliver thousands of membrane proteins to the right place at the right time. It is important for scientists to understand the molecular mechanisms underlying intracellular vesicular traffic. Associate Professor Akiko K. Satoh, at the Division of Life Science, Graduate School of Integral Arts and Science, Hiroshima University, and her collaborators have been investigating the mechanism of intracellular vesicular traffic using Drosophila photoreceptors. The team has shown that the protein Rab1 is involved in the transport of materials from the endoplasmic reticulum to Golgi, that GPI synthesis is necessary for rhodopsin sorting in the trans-Golgi network, and that the Rab11/dRip11/Myo V complex is essential for post-Golgi transport of rhodopsin.

Recently, Dr. Satoh's group performed the genome-wide screening of Drosophila mutants, and identified 233 mutants that failed to synthesize and/or transport rhodopsin to the photosensitive membrane of the rhabdomeres.

In the current study, Dr. Satoh and her collaborators showed that dPob/EMC3, EMC1, and EMC8/9—the Drosophila homologs of the subunits of ER membrane protein complex (EMC)—are essential for stabilizing the newly synthesized rhodopsin. EMC was also showed to be required for the biosynthesis of other multi-pass transmembrane proteins. However, EMC is not required for a secreted protein or type-I,

-II, and -VI single-pass transmembrane proteins. dPob/EMC3-deficient rhabdomeres undergo retinal degeneration, similar to those in rhodopsin-null Drosophila mutants. These results are published in an eLife article titled, "dPob/EMC is essential for biosynthesis of rhodopsin and other multi-membrane proteins in Drosophila photoreceptors."

Dr. Satoh said, "It is very important to understand the mechanisms underlying protein folding and integration into the cellular membrane. You may think this question is too basic; however, knowledge on cellular functioning is fundamental to life. Our next challenge will be to reveal why the EMC complex is specifically required for the functioning of multi-pass transmembrane proteins. In addition, the gene POB has not yet been implicated in retinitis pigmentosa in humans. In the future, I hope our results will contribute to the development of next-generation medical care in the treatment of retinitis pigmentosa."

More information: Satoh, A. K., Tokunaga, F., Kawamura, S. and Ozaki, K. (1997) "In situ inhibition of vesicle transport and protein processing in the dominant negative Rab1 mutant of Drosophila." *Journal of Cell Science*. 110, 2943-2853.

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