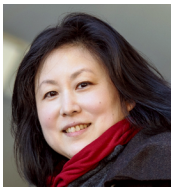
Mechanism of autophagy initiation by palmitoylation



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Abstract

Autophagy is a key cellular process that degrades and recycles damaged components to maintain cellular health and prevent disease. This study shows that the enzyme ZDHHC13 is crucial for autophagy initiation by palmitoylating ULK1, a key protein required to start autophagy. Palmitoylation helps ULK1 move from the cytoplasm to the autophagosome formation site, where it enhances phosphorylation of ATG14L, activating the PI3-kinase complex essential for autophagosome membrane production. Loss of ZDHHC13 impairs autophagy by blocking ULK1 localization and function, potentially contributing to diseases such as cancer and neurodegeneration.

Background & Results

Autophagy is a crucial intracellular self-defense mechanism by which cells degrade and recycle their own proteins and organelles in response to nutrient starvation and various stresses, thereby maintaining cellular homeostasis and viability. This process plays a significant role in a wide range of pathological conditions, including cancer, neurodegenerative diseases, and aging, making the elucidation of its initiation mechanisms essential for therapeutic strategy development. The serine/threonine kinase ULK1 is a critical driver of autophagy initiation and is typically localized in the cytoplasm; however, its proper function requires precise translocation to the endoplasmic reticulum membrane, which serves as the autophagosome formation site. In this study, we uncovered a novel molecular mechanism in which the palmitoyltransferase enzyme ZDHHC13 mediates the palmitoylation of ULK1, thereby facilitating its localization to the autophagosome formation site. This palmitoylation enables ULK1 to efficiently accumulate at the site, where it induces phosphorylation of ATG14L, a key component of the PI3K complex, resulting in the activation of the complex and triggering autophagy initiation. Conversely, ULK1 mutants deficient in palmitoylation fail to localize properly, leading to significant impairment of autophagy. Additionally, knockdown of ZDHHC13 expression markedly inhibits autophagy initiation, demonstrating that ZDHHC13-mediated palmitoylation of ULK1 is indispensable for autophagy onset. These findings advance our understanding of the molecular basis of autophagy initiation, with important implications for elucidating the pathogenesis of autophagy-related diseases and for guiding future development of novel therapeutic targets. This work also provides a fundamental basis for exploring cellular homeostasis mechanisms and stress responses at the molecular level.

Significance of the research and Future perspective

Autophagy is a vital biological process deeply involved in various diseases such as cancer, neurodegenerative disorders, and aging. This study provides novel insight into the critical role of palmitoylation in autophagy initiation and presented its regulatory mechanism systematically for the first time. Although basic research may seem to focus on detailed phenomena, it actually serves as a foundation for discovering drug targets and developing new therapies in the future. Moreover, this research holds significant social value as a fundamental study for the prevention and treatment of diseases caused by autophagy dysfunction. Even though basic research may appear to analyze minute details on the surface, understanding these molecular mechanisms accelerates the discovery of new drug targets and provides the shortest path to developing fundamental treatments, underscoring its profound societal importance.

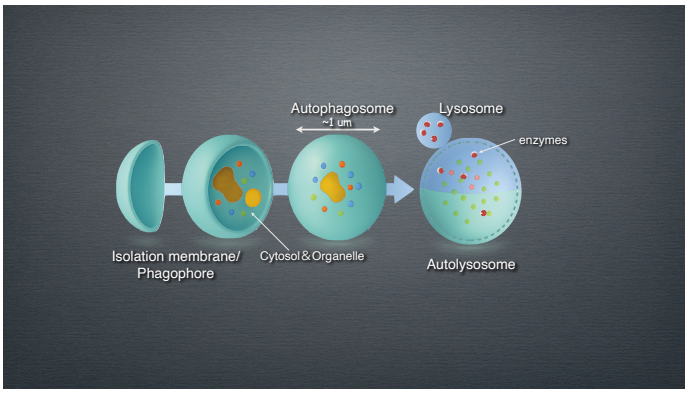

Figure 1: Process of autophagosome formation

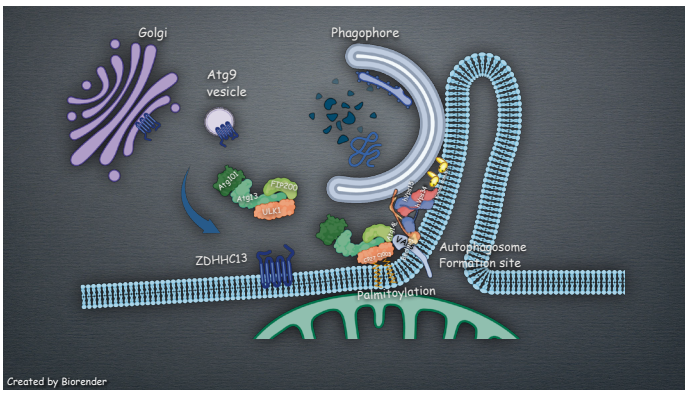

Figure 2: Mechanism of autophagy initiation via ULK1 palmitoylation

Patent	
Treatise	Tabata, Keisuke; Imai, Kenta; Hamasaki, Maho et al. Palmitoylation of ULK1 by ZDHH13 plays a crucial role in autophagy. Nature Communications. 2024, 15(1), 7194. doi: 10.1038/s41467-024-51402-w
URL	https://www.osaka-u.ac.jp/en/news/global_outlook/research_highlights/rh_01_202412 https://www.nature.com/collections/fyfvkbpslf/content/nature-cell-biology-turning-points
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