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New Drug Discovery: Use of Potent and Specific Autophagy Inhibitors by Targeting the ATG8 Family Proteins

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Background

Autophagy is responsible for degrading intracellular protein aggregates, damaged organelles and invasive pathogens, and it thus plays an essential role in maintaining cellular homeostasis and responding to stress conditions. This process is highly regulated and involves multiple steps. Dysregulation of autophagy is closely associated with a variety of human diseases such as cancers, metabolic diseases, immunity disorders and neurodegenerative diseases.

Over the past two to three decades, genetic screenings in Yeast and C. elegans have enabled researchers to identify and characterise key components of autophagy machinery, including AuTophaGy-related (Atg) genes and Ectopic P Granules (Epg) genes. One of these genes, Atg8, is involved in multiple steps of the autophagic process and is considered a central component in autophagy. Due to the central role of Atg8s in autophagy, it is desirable to develop potent and highly selective Atg8 binding peptides, as these will be remarkably valuable for numerous applications. For instance, they can be used to efficiently inhibit Atg8-mediated selective autophagy spatiotemporally in living animals, to clearly delineate functions of different Atg8 members in autophagy and to monitor autophagy process by specifically recognising each Atg8 member.

Technology Overview

Mammalian Atg8 family proteins are central drivers of autophagy and contain six members, classified into the LC3 and GABARAP subfamilies. Due to their high sequence similarity and consequent functional overlaps, it is difficult to delineate the specific functions of Atg8 proteins in autophagy. We find a strong GABARAP-selective inhibitory peptide harboured in 270/480 kD ankyrin-G and a potent pan-Atg8 inhibitory peptide naturally occurring in 440 kD ankyrin-B. Structural studies elucidate the mechanism governing the Atg8 binding potency and selectivity of the peptides, reveal a general Atg8-binding sequence motif, and allow development of a more GABARAP-selective inhibitory peptide. These peptides effectively block autophagy when expressed in cultured cells. Expression of these ankyrin-derived peptides in C. elegans also inhibits autophagy, causing accumulation of the p62 homolog SQST-1, delayed development and accelerated ageing. The inhibitory peptides can serve as leads to develop drugs for cancer or other autophagy-related disease treatments. The inhibitory peptides can also be used to screen for autophagy inducers, which are potential drug leads for treating neurodegenerative diseases such as Alzheimer's disease, Parkinson disease, and other autophagy-related diseases. The Ank-derived peptides can also be used as specific markers to monitor the occurrence of autophagy.

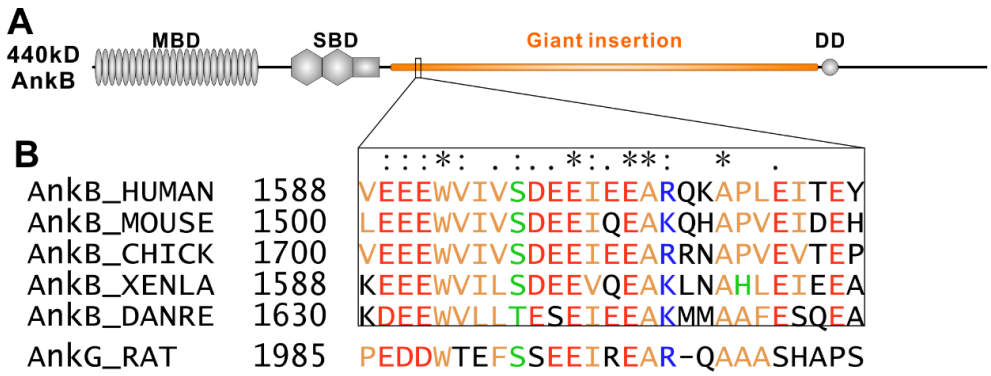
Applications

- Development of drugs for potential cancer or other autophagy-related disease treatments Object tracking in hospitals and warehouses
- Use in research and drug screening as a tool to screen for autophagy inducers
- Use as specific markers to monitor the occurrence of autophagy

Patents

- PCT Patent no.: PCT/CN2018/113894
- US Patent Pending: -
- China Patent Pending: -

Figures



(A) Diagram showing the domain organisations of 440 kD AnkB and the locations of the extended LIR sequence in the giant AnkB only. (B) Sequence alignment of AnkB LIR in vertebrates. AnkG LIR is also included as a reference.

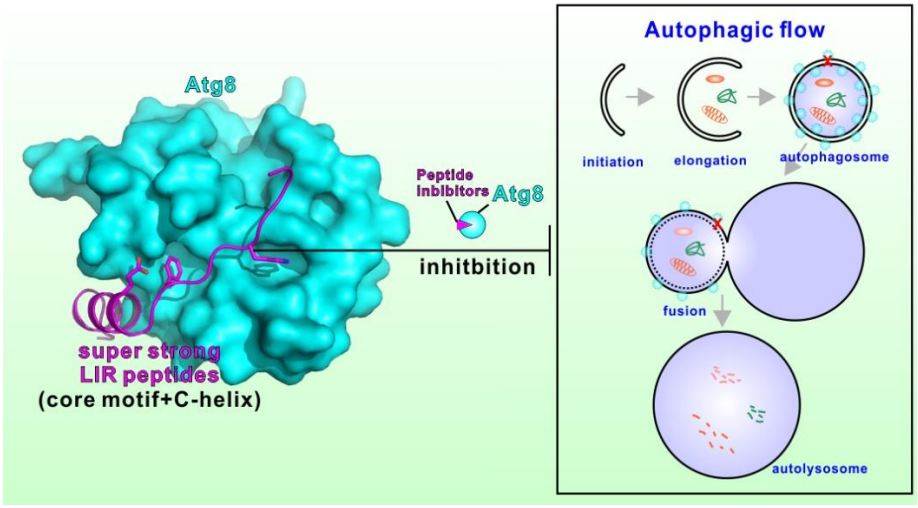


Diagram showing the working mechanism.