Autophagy and Bacterial Infection: a Competition for Survival

PhD student: Ying, YANG
Supervisor: Professor Margaret IP
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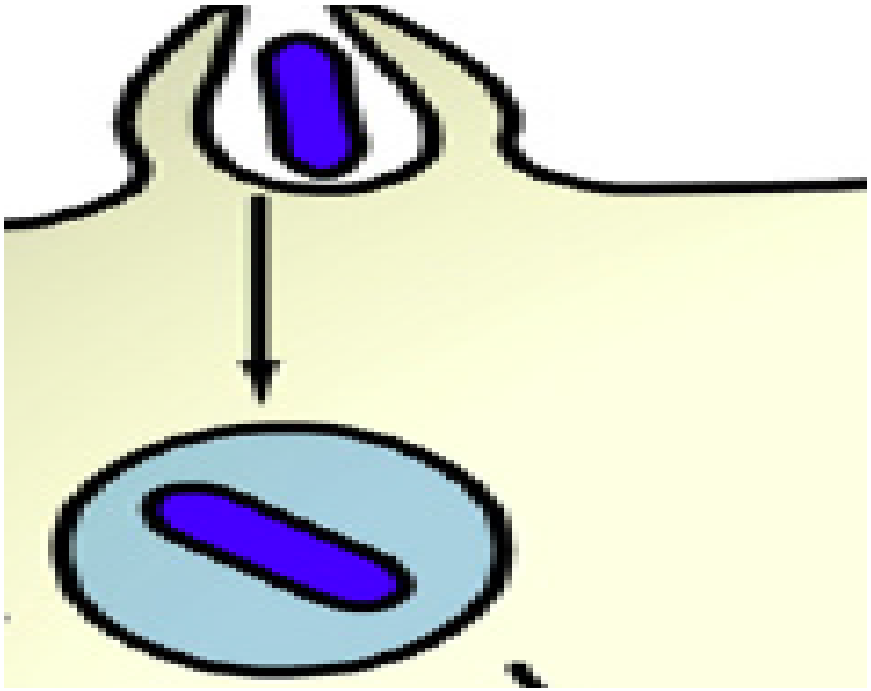
Department: Microbiology, CUHK

Autophagy: an essential conserved lysosomal degradation pathway

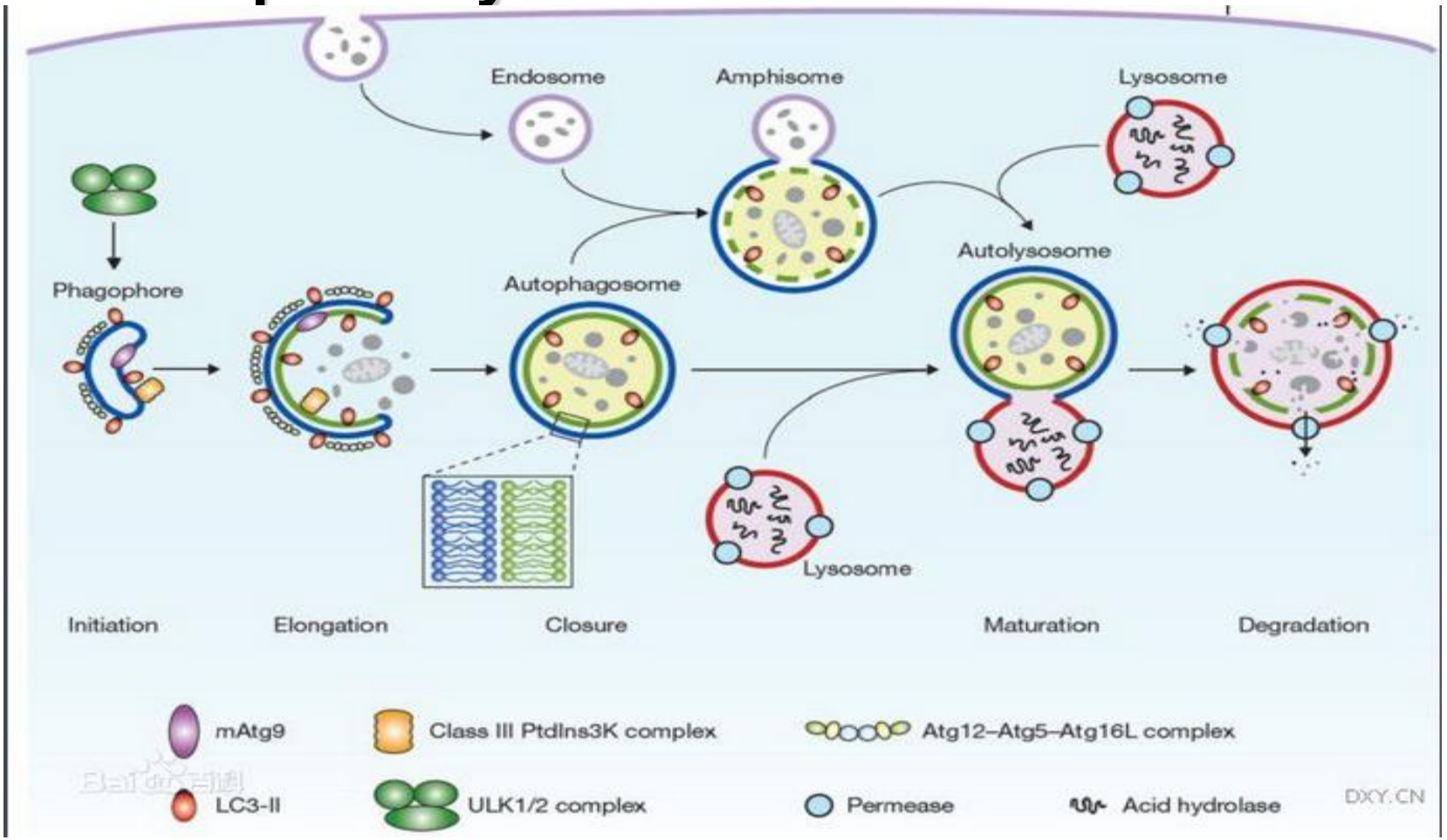
Numerous pathogens have developed the capacity to invade host cells to be protected from components of the systemic immune system.



Autophagy: an essential conserved lysosomal degradation pathway

- Autophagy is an intracellular process delivering cytoplasmic material to the lysosome for degradation.
- The cellular events of this ancient and highly conserved process: phagophore- autophagosome- autolysosome and degrade the enclosed material.
- Autophagy acts as a cytoplasmic quality control mechanism, eliminating protein aggregates, damaged organelles and intracellular microbes to maintain cellular homeostasis.

Autophagy: an essential conserved lysosomal degradation pathway



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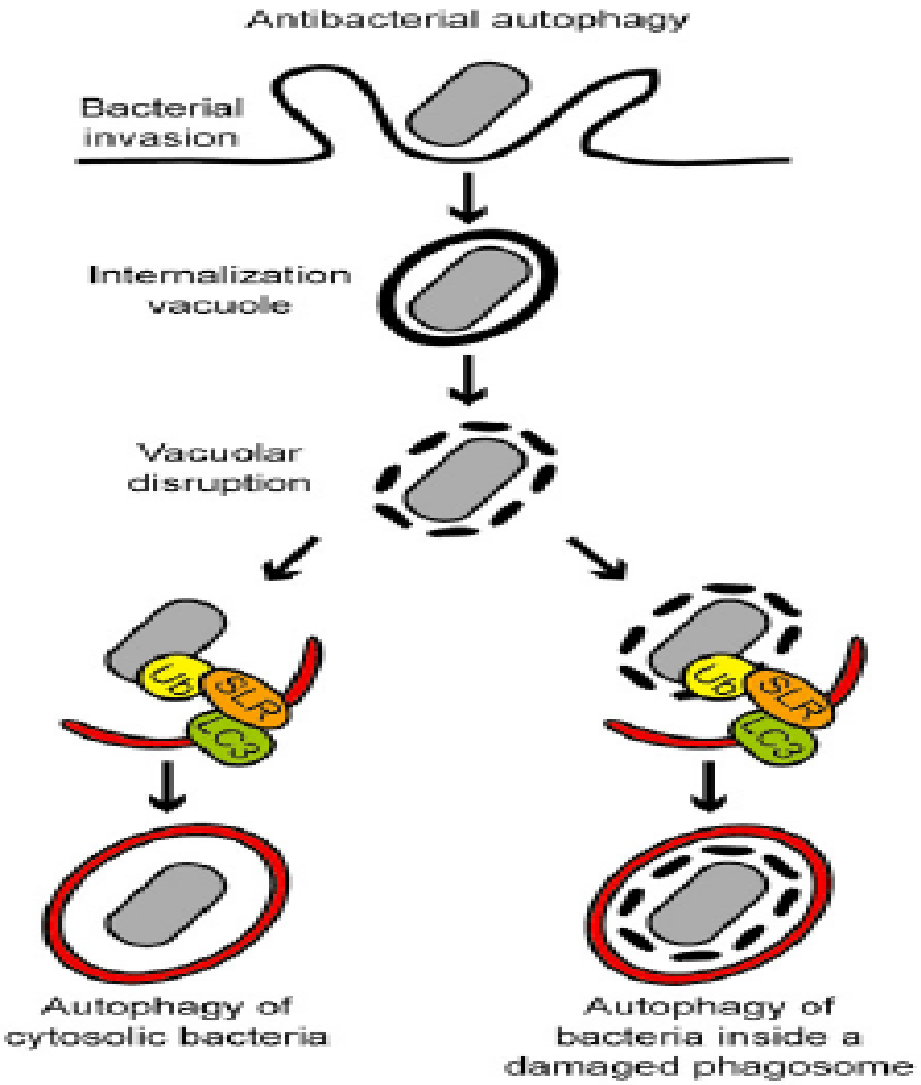
Autophagy: different roles during different bacterial infections

- Antibacterial autophagy: restrict bacterial replication.
- Non-bacterial autophagy: cross-talk with innate immune signaling pathways.
- Pro-bacterial autophagy: support bacterial replication.

Antibacterial autophagy: restrict bacterial replication



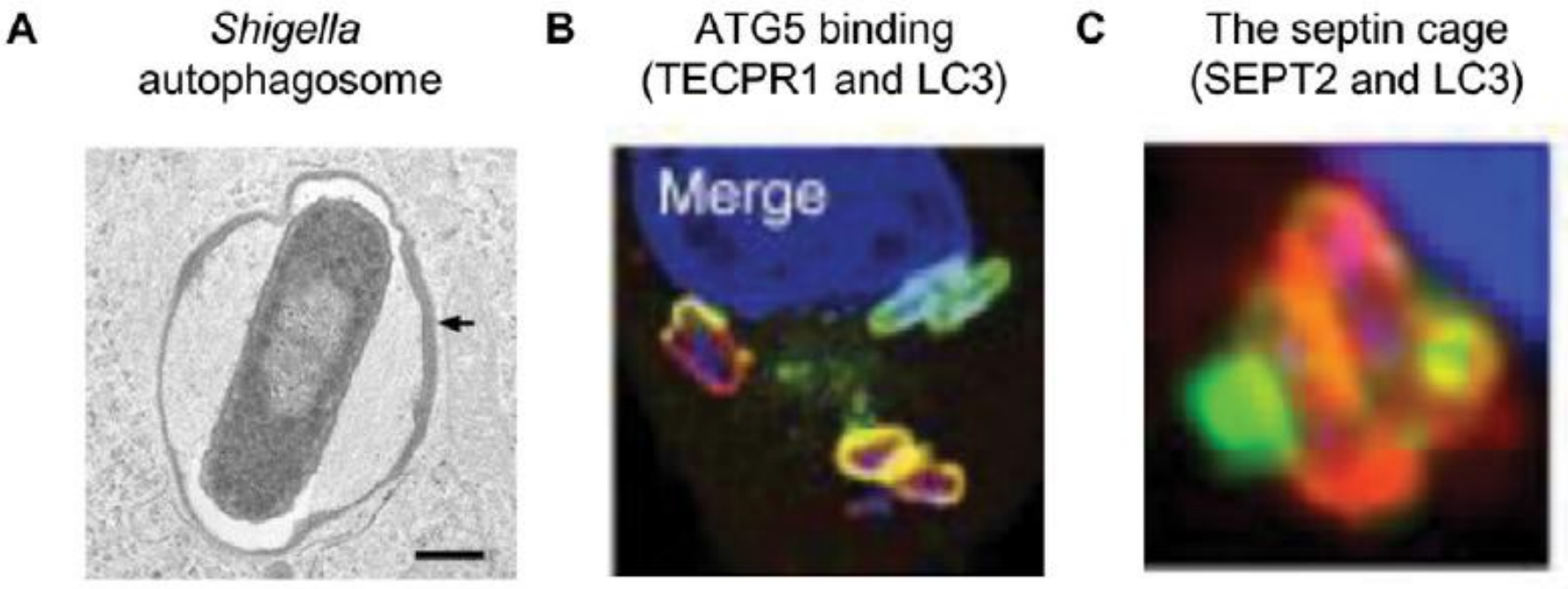
Mostowy S. Autophagy and bacterial clearance: a not so clear picture[J]. Cellular microbiology, 2013, 15(3): 395-402.

Antibacterial autophagy: Shigella clearence

- Autophagy of **Shigella** is triggered by ATG5 recognition of IcsA and is mediated by TECPR1, a Tectonin domain-containing protein, which binds to ATG5 and promotes autophagosome–lysosome fusion.

- To restrict bacterial motility and autophagy escape, septins are guanosine triphosphate (GTP) binding proteins recruited to sites of IcsA-induced actin polymerization, and form cage-like structures.

Antibacterial autophagy: Shigella clearence



Mostowy S. Autophagy and bacterial clearance: a not so clear picture[J]. Cellular microbiology, 2013, 15(3): 395-402.

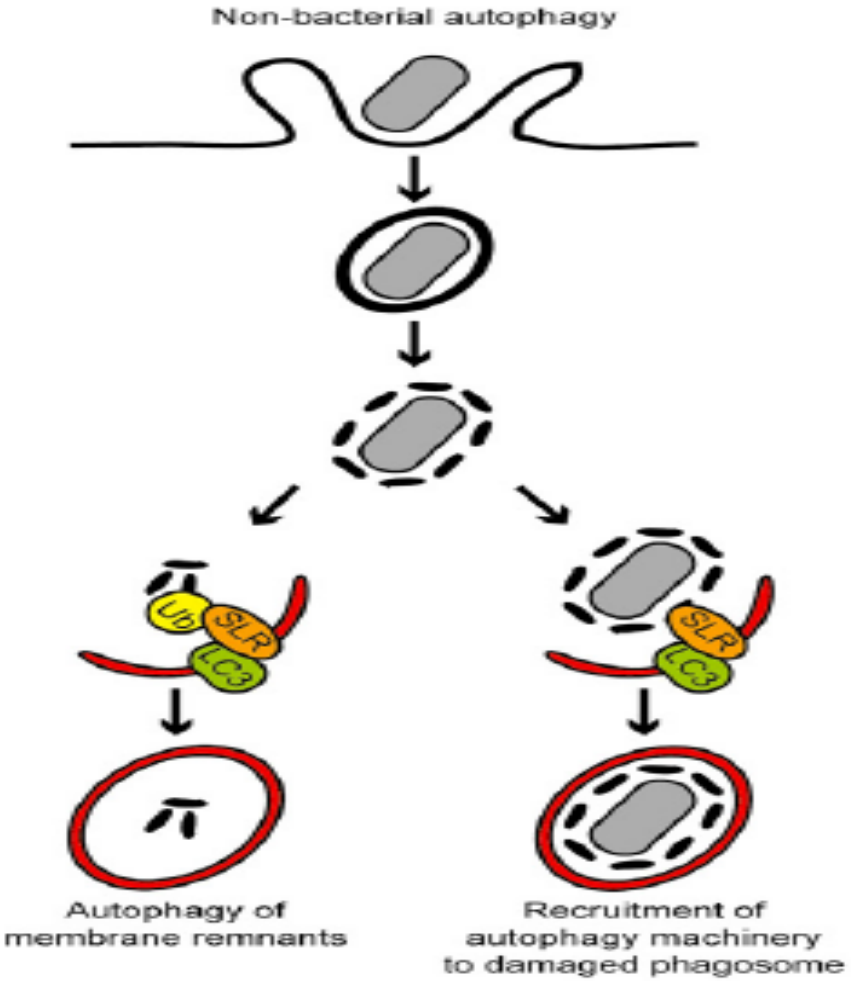
Antibacterial autophagy: Mycobacterium tuberculosis clearence

- Mycobacterium tuberculosis is a vacuolar pathogen that survives within macrophages by arresting phagosomal maturation.

- Autophagy induction counteracts the maturation block imposed by mycobacterium.

- A variety of studies have shown that the induction of autophagy by starvation, inhibition of mTOR (a suppressor of autophagy), vitamin D and interferon-gamma (IFNγ) may help restrict mycobacterial replication. p62 appears to be crucial for this process, and provides mycobacterial autophagolysosomes with enhanced antimicrobial capacities relative to conventional phagolysosomes.

Non-bacterial autophagy : cross-talk with innate immune signaling pathways



Mostowy S. Autophagy and bacterial clearance: a not so clear picture[J]. Cellular microbiology, 2013, 15(3): 395-402.

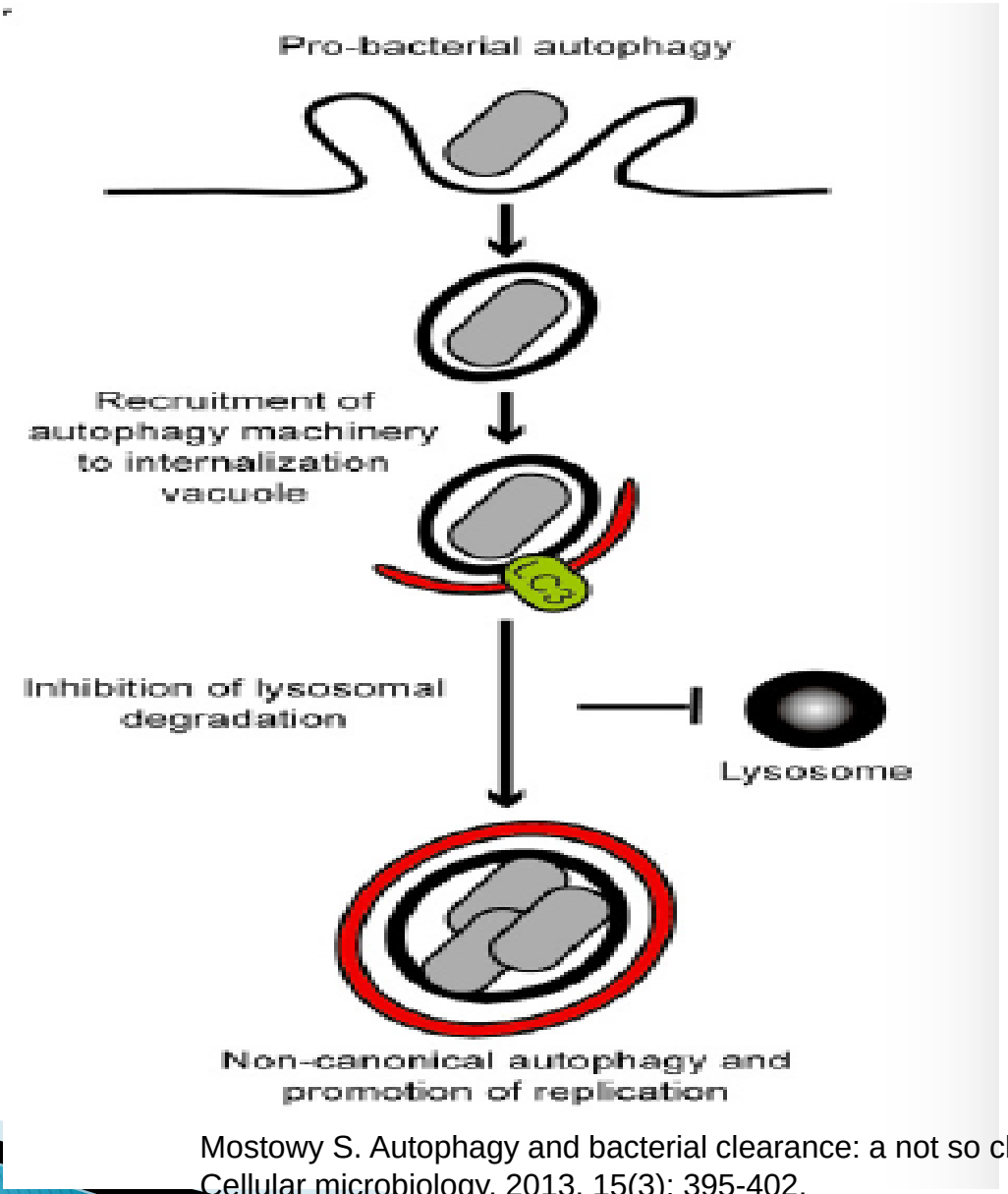
Non-bacterial autophagy : cross-talk with innate immune signaling pathways

- Studies using Shigella have shown that in the cytosol of infected cells, membrane remnants induced by invading Shigella are ubiquitinated and recognized by p62, NBR1 and NDP52 for delivery to autophagosomes.

- Inflammasome components, localized to damaged membranes, are also ubiquitinated and recognized by p62 for autophagy.

- The studies with V.cholerae cytolysin (VCC) the pore-forming toxin indicate that the toxin triggers an autophagic response in the target cell, and demonstrate that autophagy acts as a cellular defense pathway against a secreted bacterial toxin.

Pro-bacterial autophagy: support bacterial replication



Mostowy S. Autophagy and bacterial clearance: a not so clear picture[J]. Cellular microbiology, 2013, 15(3): 395-402.

Pro-bacterial autophagy: support the replication of Brucella

- **Brucella** may co-opt autophagosome initiation factors ATG1 (ULK1), Beclin1 and ATG14 to convert Brucella-containing vacuoles (BCVs) into autophagosome-like compartments called autophagic BCVs (aBCVs).

- A non-canonical autophagy pathway here promotes bacterial replication and survival since autophagosome elongation factors ATG4B, ATG5, ATG7, LC3B and ATG16L1 are not required for biogenesis of aBCVs.

Pro-bacterial autophagy: support the replication of S. aureus

- **S. aureus** is a Gram-positive bacterium that can invade cells and replicate in autophagosome-like vacuoles. Hla (α-haemolysin), a pore-forming toxin secreted by S. aureus, is required for the recruitment of LC3, suggesting the recruitment of autophagy components by Hla.

- Hla-induced autophagy requires ATG5, but does not require Beclin1 (ATG6) nor PI3 kinase activity, highlighting the benefit of a non-canonical autophagy pathway for S. aureus replication.

Perspectives

- Autophagy acts as an innate cytoplasmic surveillance mechanism: enables the host cell to remove pathogens, and to subsequently deliver them to the degradative lysosomal compartment.

- Pathogens have developed different strategies to avoid this pathway.

- Many key points remain to be solved, the search for virulence factors and the elucidation of how they control the autophagy machinery will be the basis of novel therapeutic intervention against intracellular pathogens.

Perspectives

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Rapamycin, Autophagy, and Alzheimer's Disease

Zhiyou Cai[a,*] and Liang-Jun Yan[b]

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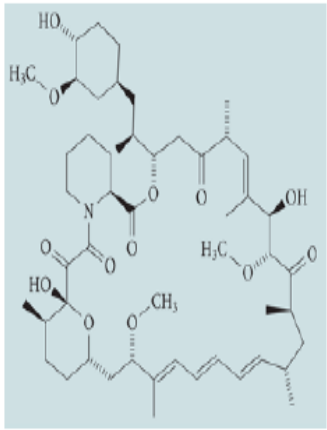
Abstract

Alzheimer's disease (AD) is a neurodegenerative disord
multiple pathological lesions. At the molecular level, AI
production and tau hyper-phosphorylation. Hence, pharn
accumulation and tau hyper-phosphorylation have poten
inhibitor of mammalian target of rapamycin (mTOR), is
agents. It is neuroprotective in neurodegenerative diseas
enhancement of autophagy, a biological process that not only facilitates the clearance of mutant proteins but also significantly reduces the build-up of toxic protein aggregates such as Aβ. Since rapamycin enhancement of autophagy has been associated with abrogation of AD pathological processes such as clearance of Aβ and neurofibrillary tangles (NTFs) as well as reduction of tau hyper-phosphorylation and

Compounds	Company	Structure	Mechanism of action
Autophagy inducers			
Rapamycin	Sigma-Aldrich		Induces autophagy by inhibiting mTORC1

Perspectives

Human Molecular Genetics, 2010, Vol. 19, No. 11 *2144–2153*
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Advance Access published on February 27, 2010

Rilmenidine attenuates toxicity of polyglutamine expansions in a mouse model of Huntington's disease

Claudia Rose[1], Fiona M. Menzies[1], Maurizio Renna[1], Abraham Acevedo-Arozena[2], Silvia Corrochano[2], Oana Sadiq[1], Steve D. Brown[2] and

[1]Department of Medical Genetics, University of Cambridge, Cambric
Hospital, Hills Road, Cambridge CB2 0XY, UK and [2]Medical Rese
Oxfordshire, UK

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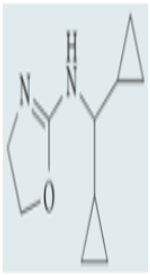
**Huntington's disease (HD) is an autosomal dominant neurodeg
expansion in huntingtin. There are no treatments that are kno
this mutation. Mutant huntingtin causes disease via a toxic gai
sity to aggregate and form intraneuronal inclusions. One therapeutic approach for HD is to enhance the degradation of the mutant protein. We have shown that this can be achieved by upregulating autophagy, using the drug rapamycin. In order to find safer ways of inducing autophagy for clinical purposes, we previously screened United States Food and Drug Administration-approved drugs for their autophagy-stimulating potential. This screen suggested that rilmenidine, a well tolerated, safe, centrally acting anti-hypertensive drug, could induce autophagy in cell culture via a pathway that was independent of the mammalian target of rapamycin. Here we have shown that rilmenidine induces autophagy in mice and in primary neuronal culture. Rilmenidine administration attenuated the signs of disease in a HD mouse model and reduced levels of the mutant huntingtin fragment. As rilmenidine has a long safety record and is designed for chronic use, our data suggests that it should be considered for the treatment of HD and related conditions.**

Rilmenidine* Tocris Bioscience



Lowers cAMP levels

Perspectives

NATURE | ARTICLE

日本語要約

Identification of a candidate therapeutic autophagy-inducing peptide

Tat beclin1

Sanae Shoji-Kawata, Rhea Sumpter, Matthew Leveno, Grant R. Campbell, Zhongju Zou, Lisa Kinch, Angela D. Wilkins, Qihua Sun, Kathrin Pallauf, Donna MacDuff, Carlos Huerta, Herbert W. Virgin, J. Bernd Helms, Ruud Eerland, Sharon A. Tooze, Ramnik Xavier, Deborah J. Lenschow, Ai Yamamoto, David King, Olivier Lichtarge, Nick V. Grishin, Stephen A. Spector, Dora V. Kaloyanova & Beth Levine

Affiliations | Contributions | Corresponding author

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Thank you!

References

- Mowers E E, Sharifi M N, Macleod K F. Novel insights into how autophagy regulates tumor cell motility[J]. Autophagy, 2016, 12(9): 1679-1680.
- Joffre C, Codogno P, Fanto M, et al. STK38 at the crossroad between autophagy and apoptosis[J]. Autophagy, 2016, 12(3): 594-595.
- Wang R C, Wei Y, An Z, et al. Akt-mediated regulation of autophagy and tumorigenesis through Beclin 1 phosphorylation[J]. Science, 2012, 338(6109): 956-959.
- Wild P, Farhan H, McEwan D G, et al. Phosphorylation of the autophagy receptor optineurin restricts Salmonella growth[J]. Science, 2011, 333(6039): 228-233.
- Chen D, Fan W, Lu Y, et al. A mammalian autophagosome maturation mechanism mediated by TECPR1 and the Atg12-Atg5 conjugate[J]. Molecular cell, 2012, 45(5): 629-641.
- Deretic V. Autophagy as an innate immunity paradigm: expanding the scope and repertoire of pattern recognition receptors[J]. Current opinion in immunology, 2012, 24(1): 21-31.
- Mostowy S. Autophagy and bacterial clearance: a not so clear picture[J]. Cellular microbiology, 2013, 15(3): 395-402.
- Yuk J M, Yoshimori T, Jo E K. Autophagy and bacterial infectious diseases[J]. Experimental & molecular medicine, 2012, 44(2): 99-108.

References

- Nakahira K, Haspel J A, Rathinam V A K, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome[J]. Nature immunology, 2011, 12(3): 222-230.
- Sakurai A, Maruyama F, Funao J, et al. Specific behavior of intracellular Streptococcus pyogenes that has undergone autophagic degradation is associated with bacterial streptolysin O and host small G proteins Rab5 and Rab7[J]. Journal of Biological Chemistry, 2010, 285(29): 22666-22675.
- Takeda K, Akira S. TLR signaling pathways[C]//Seminars in immunology. Academic Press, 2004, 16(1): 3-9.
- Rubinsztein D C, Codogno P, Levine B. Autophagy modulation as a potential therapeutic target for diverse diseases[J]. Nature reviews Drug discovery, 2012, 11(9): 709-730.
- Levine B, Packer M, Codogno P. Development of autophagy inducers in clinical medicine[J]. The Journal of clinical investigation, 2015, 125(1): 14-24.
- Campoy E, Colombo M I. Autophagy in intracellular bacterial infection[J]. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 2009, 1793(9): 1465-1477.
- Autophagy modulation as a potential therapeutic target for diverse diseases
- Johansen T, Lamark T. Selective autophagy mediated by autophagic adapter proteins[J]. Autophagy, 2011, 7(3): 279-296.