AUTOPHAGY
2017, VOL. 13, NO. 2, 223–224
http://dx.doi.org/10.1080/15548627.2016.1267075

Taylor & Francis
Taylor & Francis Group

EDITOR'S CORNER

Xenophagy: A battlefield between host and microbe, and a possible avenue for cancer treatment

Kai Mao[a,b] and Daniel J. Klionsky[a]

[a]Life Sciences Institute and Department of Molecular, Cellular and Developmental Biology, University of Michigan, Ann Arbor, MI, USA; [b]Present address: Department of Molecular Biology, Massachusetts General Hospital, and Department of Genetics, Harvard Medical School, Boston, MA, USA

ABSTRACT

In eukaryotes, xenophagy is defined as a type of selective macroautophagy/autophagy that is used for eliminating invading pathogens. In contrast to other types of selective autophagy, such as mitophagy, pexophagy and ribophagy, xenophagy is used by eukaryotes for targeting microbes—hence the prefix "xeno" meaning "other" or "foreign"—that have infected a host cell, leading to their lysosomal degradation. This unique characteristic links xenophagy to antibacterial and antiviral defenses, as well as the immune response. Furthermore, recent studies suggest a complicated role of xenophagy in cancer, through either suppressing tumorigenesis or promoting survival of established tumors. In this issue, Sui et al. summarize previous and current studies of xenophagy and consider them in the context of anticancer treatment.

ARTICLE HISTORY
Received 28 November 2016
Revised 28 November 2016
Accepted 28 November 2016

KEYWORDS
autophagy; bacteria; cancer; host; xenophagy

The history of xenophagy[1] can be traced back to at least 1984, when Rikihisa reported that infection of the bacterium *Rickettsiae* could dramatically induce autophagosome formation in polymorphonuclear leukocytes of guinea pigs;[2] the implications of this observation were not fully understood at the time because genetic studies of autophagy had not yet revealed the identity of the autophagic molecular machinery. Subsequent work suggested that in addition to its canonical role in self-eating, autophagy is also able to capture invasive bacteria, thus safeguarding the health of host cells. During the past 3 decades, an increasing number of bacteria have been found to be the participants in the "xenophagy battlefield," where both host cells and microbes evolve in a constant struggle for supremacy; we use the term "battlefield" to denote the fact that even though the host cells direct and manage xenophagy, they cannot always dominate the battle and eliminate the invaders.

A variety of well-known human pathogens are rapidly detected after infection, and efficiently captured by phagophores, leading to their enclosure within autophagosomes and subsequent digestion in lysosomes. For example, when infective *Salmonella typhimurium* appear in the cytosol of host cells the bacterial surface becomes polyubiquitinated, allowing recognition by the receptor/scaffold protein SQSTM1/p62. The interaction between SQSTM1 and LC3 connects the bacteria to the phagophore, which is followed by the formation of autophagosomes surrounding the bacteria.[3] Additional bacteria, such as *Streptococcus pyogenes, Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa*, will typically lose the "battle" and be eliminated by xenophagy. Thus, xenophagy is a powerful system for eliminating pathogens and protecting the host cells from fatal damage.

Some microbes, however, develop special strategies to block or evade the xenophagic response. These bacteria are able to secrete proteins that disrupt the detection of the bacteria or inhibit autophagosome formation. One example of such bacteria is *Shigella flexneri*. After infection, *S. flexneri* secrets IcsA/VirG to promote intracellular actin-based motility; however, the bacterial surface protein IcsA can be recognized by ATG5, triggering xenophagy. *S. flexneri* therefore also secretes IcsB to interfere with this detection, by competing for ATG5 binding, and thus escaping from xenophagy.[4] Other bacteria using similar mechanisms of evasion include *Listeria monocytogenes* and *Legionella pneumophila*.

Microbial adaptations to xenophagy display yet another twist in that certain pathogens can actively trigger this process, subsequently residing within autophagosomes to protect them from a further host response, allowing propagation within the cytoplasm. *Staphylococcus aureus* is a significant human pathogen that secretes a pore-forming toxin, α-hemolysin, to activate autophagy. After being engulfed within autophagosomes, *S. aureus* inhibits autophagosome maturation and fusion with lysosomes, thereby hiding in "armor" provided by the host cell.[5,6] Other bacteria that carry out similar modes of infection include *Coxiella burnetii, Anaplasma phagocytophilum*, and uropathogenic *Escherichia coli*.

Recent studies have begun to reveal the role of xenophagy in bacteria-associated cancer. *Helicobacter pylori*, a gram-negative bacterium, is able to infect gastric epithelial cells, and severe and prolonged infection causes inflammation and gastric carcinogenesis.[7] Individuals with a xenophagy defect due to mutation of ATG16L1 have a higher risk of *H. pylori* infection and gastric cancer, suggesting a protective role of xenophagy in prevention of tumorigenesis.[8] Conversely, established tumors take advantage of xenophagy to prevent bacterial infection and promote cancer cell growth. For example, *S. typhimurium* is able to infect

CONTACT Daniel J. Klionsky klionsky@umich.edu University of Michigan; Life Sciences Institute, Rm. 6036, 210 Washtenaw Ave., Ann Arbor, MI 48109-2216, USA.

tumor cells and slow down the tumor growth; thus, cancer cells with a xenophagy defect due to knockdown of ATG5 or BECN1 show increased sensitivity to *S. typhimurium*, suggesting the possibility of a combined anticancer treatment that blocks xenophagy and targets cancer cells for bacterial infection.[9]

Although antimicrobial drugs such as anthracyclines are already in use as antitumor agents,[10] it is not known if they act by inducing xenophagy. Similarly, there is currently no direct evidence showing a protective role for xenophagy in preventing cancer. However, the fight between eukaryotic hosts and microbes provides one example of the evolutionary adaptations and counter-adaptations that are mediated in part through xenophagy, and this battle will continue, likely providing novel twists that we cannot yet anticipate. Thus, determining how to use bacteria and xenophagy for cancer therapy is an attractive area for further study by researchers and clinicians.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by Damon Runyon postdoctoral fellowship DRG-2213-15 to KM, and NIH grant GM053396 to DJK. The authors thank Dr. Hongming Pan for helpful comments.

ORCID

Daniel J. Klionsky http://orcid.org/0000-0002-7828-8118

References

[1] Levine B. Eating oneself and uninvited guests: autophagy-related pathways in cellular defense. Cell 2005; 120:159-62; PMID:15680321

[2] Rikihisa Y. Glycogen autophagosomes in polymorphonuclear leukocytes induced by rickettsiae. Anatomical Record 1984; 208:319-27; PMID:6721227; http://dx.doi.org/10.1002/ar.1092080302

[3] Zheng YT, Shahnazari S, Brech A, Lamark T, Johansen T, Brumell JH. The adaptor protein p62/SQSTM1 targets invading bacteria to the autophagy pathway. J Immunol 2009; 183:5909-16; http://dx.doi.org/10.4049/jimmunol.0900441

[4] Ogawa M, Yoshimori T, Suzuki T, Sagara H, Mizushima N, Sasakawa C. Escape of intracellular Shigella from autophagy. Science 2005; 307:727-31; PMID:15576571; http://dx.doi.org/10.1126/science.1106036

[5] Schnaith A, Kashkar H, Leggio SA, Addicks K, Kronke M, Krut O. Staphylococcus aureus subvert autophagy for induction of caspase-independent host cell death. J Biol Chem 2007; 282:2695-706; PMID:17135247; http://dx.doi.org/10.1074/jbc.M609784200

[6] Mestre MB, Fader CM, Sola C, Colombo MI. Alpha-hemolysin is required for the activation of the autophagic pathway in Staphylococcus aureusinfected cells. Autophagy 2010; 6:110-125; PMID:20110774; http://dx.doi.org/10.4161/auto.6.1.10698

[7] Greenfield LK, Jones NL. Modulation of autophagy by Helicobacter pylori and its role in gastric carcinogenesis. Trends Microbiol 2013; 21:602-12; PMID:24156875; http://dx.doi.org/10.1016/j.tim.2013.09.004

[8] Castano-Rodriguez N, Kaakoush NO, Goh KL, Fock KM, Mitchell HM. Autophagy in Helicobacter pylori infection and related gastric cancer. Helicobacter 2015; 20:353-69; PMID:25664588; http://dx.doi.org/10.1111/hel.12211

[9] Liu B, Jiang Y, Dong T, Zhao M, Wu J, Li L, Chu Y, She S, Zhao H, Hoffman RM, et al. Blockage of autophagy pathway enhances Salmonella tumor-targeting. Oncotarget 2016; 7:22873-82; PMID:27013582

[10] Booser DJ, Hortobagyi GN. Anthracycline antibiotics in cancer therapy. Focus on Drug Resistance. Drugs 1994; 47:223-58.