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EDITOR'S CORNER

Where is the field of autophagy research heading?

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ABSTRACT
In this editors' corner, the section editors were asked to indicate where they see the autophagy field heading and to suggest what they consider to be key unanswered questions in their specialty area.

Hagai Abeliovich

Mitophagy

The selective degradation of mitochondria through macroautophagy, usually abbreviated as mitophagy, is a central housekeeping function in most eukaryotic cells. Defects in mitophagy have been linked to degenerative and metabolic disease states, and induction of mitophagy plays a role in developmental transitions in metazoans. Broadly, two types of molecular mechanisms have been linked to mitophagy. In one type, ubiquitination of outer and inner mitochondrial membrane proteins is linked to the autophagic machinery via bifunctional receptor proteins that interact both with ubiquitin (or phospho-ubiquitin) as well as with elements of the autophagic machinery such as LC3/Atg8. In the second type, a more classical "autophagy receptor" is localized to the target mitochondrion and directly binds elements of the autophagic machinery. While the mechanism of the first class, typified by the PINK1-PRKN axis, has been widely studied at the molecular level, much less is known about the mechanisms and function of the second, ubiquitin-independent, class of mitophagy pathways.

I think that these are exciting times in mitophagy research because there are so many unanswered questions. The following represent a sample:

1. Why is there such a proliferation of mitophagy receptors? Do these reflect cell-type or tissue specificity, specificity to mitochondrial subtypes, or specificity to the activation trigger?

2. Does the role of mitophagy in developmental transitions simply reflect a metabolic shift between respiratory and glycolytic lifestyles, or are there more subtle and complicated explanations?

3. Is quality control mitophagy a random event that is triggered by stochastic malfunction of a single mitochondrion? If so, then is the cell sacrificing a plethora of perfectly functioning molecules just to get rid of a few bad apples (the "Sodom and Gomorrah" paradox)?

4. Is mitophagy linked to mitochondrial heterogeneity? Mitochondrial heterogeneity is an acknowledged yet understudied phenomenon wherein the same cell may harbor mitochondria with different compositions, physiological functions, etc. Do different types of mitophagy act on different subpopulations within the mitochondrial network?

5. What is the relationship between mitochondrial fission-fusion dynamics and mitophagy? The number of opinions on this question seems to be at least equal to the number of papers on the subject, with opinions ranging from discounting fission-fusion dynamics as a driving or permissive factor altogether, to arguments that fission is essential for mitophagy or that it is even a rate limiting step.

6. What is the interplay between mitophagy and other mitochondrial quality control pathways?

7. Can pharmacological modulation of mitophagy play a therapeutic role in treating mitochondrial pathologies?

Jayanta Debnath

Cancer

Despite continued clinical interest in targeting macroautophagy/autophagy to treat cancer, many uncertainties remain due to the multifaceted roles that autophagy plays during initiation, progression and metastasis [1,2]. Most attention in recent years has focused on inhibiting either autophagy or lysosomal function in advanced tumors due to the critical roles that autophagy plays in tumor cell survival and fitness, including nutrient scavenging, cell growth and metabolic adaptation. Indeed, certain tumors, most notably those with

oncogenic mutations that rewire cellular metabolism (e.g., mutant RAS, BRAF, STK11/LKB) have proven highly sensitive to autophagy inhibition in diverse in vivo preclinical models [2]. Nevertheless, we have also learned that tumor cells rapidly develop resistance to autophagy inhibition [3] and that in certain advanced cancers, autophagy inhibition can unexpectedly promote metastatic outgrowth and recurrence [4]. Hence, over the upcoming years, two important areas for future research will be to further scrutinize how tumor cells adapt to autophagy inhibition and to delineate strategies to target autophagy without untoward effects on metastasis.

Thinking beyond autophagy in tumor cells themselves, one of the most exciting developments in recent years has been the increasing appreciation of the roles that autophagy in host tissues plays in modulating cancer progression, response to therapy, and the immune recognition of tumors [1,5]. A number of studies have uncovered new functions for autophagy in the control of host-tumor metabolic exchange, the regulation of tumor cell immunity, and in the generation of stromal microenvironments permissive for tumor growth. Further defining these cardinal features of the host autophagic response to tumors and determining how they can be leveraged for therapeutic benefit remains an important area for investigation in the upcoming years.

Finally, from a therapeutic standpoint, the repurposing of hydroxychloroquine in clinical trials over the last decade has broached the promise of autophagy inhibition as a therapeutic strategy but also revealed its pharmacological limitations in humans [1]. Overall, these studies point to two fundamental needs in the upcoming years in order to effectively target autophagy in cancer patients. First, we require new chemical matter to specifically stimulate or inhibit autophagy in humans and to further understand how to best utilize such agents therapeutically during the various stages of cancer progression. Second, we require noninvasive strategies to monitor autophagy in cancer patients.

Wen-Xing Ding

Metabolism

As a catabolic pathway for proteins, lipids, carbohydrates and nucleic acids to produce amino acids, fatty acids, sugars and nucleosides, macroautophagy/autophagy is a major contributor to cellular metabolism for cell survival and remodeling. As such, autophagy has been implicated in normal development, physiology and various metabolic diseases such as insulin resistance, obesity, diabetes, nonalcoholic fatty liver disease (NAFLD), neurodegenerative disease and cancer [6–8]. While the evidence of autophagy in regulating metabolism is compelling, there are several unanswered key questions for autophagy in metabolism and metabolic diseases for future studies.

Autophagy is a highly dynamic process. The breakdown of metabolites such as amino acids and fatty acids from autophagic degradation also generates potent autophagy inhibitors, which thus establish a feedback inhibition loop on

autophagy. Whether and how the metabolite-mediated feedback inhibition on autophagy fine tunes the balance of autophagy for the homeostasis of metabolic tissues has not been well elucidated.

Despite decades of research, safe pharmacological modulators (inducers and inhibitors) of autophagy in the prevention and treatment of metabolic diseases are still lacking. Some autophagy inducers such as metformin, rapamycin, trehalose and imatinib or autophagy inhibitors such as chloroquine and hydroxychloroquine, have been tested on animal models of diabetes, NAFLD and cancer [9]. However, these autophagy modulators may have multiple other targets in addition to targeting autophagy. High-throughput screening with follow-up validation of new autophagy modulators using genetic autophagy mouse models that have high (*rubcn* knockout mice) or low (*Becn1*$^{+/-}$ or tissue-specific *atg5* knockout mice) autophagy activity in metabolic tissues may be helpful to identify more specific safe autophagy modulators for preventing and treating metabolic diseases.

Whereas activation of autophagy is generally beneficial for most metabolic tissues, increased autophagy may favor cancer cell survival and proliferation [10]. Defective autophagy in hepatocytes causes accumulation of damaged mitochondria and dysregulation of lipid and xenobiotic metabolism resulting in hepatomegaly, liver injury and spontaneous liver cancer [11–14]. However, autophagy favors the activation of hepatic stellate cells that contributes to liver fibrosis [15,16], a process that also results in the accumulation of excess extracellular matrix proteins and collagen in many chronic liver diseases. How to identify tissue or cell-specific autophagy modulators is a challenging task for future studies.

There are dynamic cross-talks and communications between different metabolic tissues and/or organs via circulating endocrine hormones, cytokines, metabolites and exosomes secreted from these tissues. Disrupted or altered organ-organ communications have bene implicated in metabolic diseases [17]. Secretory autophagy plays a critical role in facilitating unconventional secretion of cytosolic cargos for intracellular and organ-organ crosstalk [18]. How cells differentially regulate degradative autophagy versus secretory autophagy is another demanding question to be investigated.

William T. Jackson

Virology

For years the virology field has struggled with understanding how viruses interact with the machinery of macroautophagy/autophagy. Frequently, the literature will claim a particular virus induces "autophagy," or benefits from "autophagy." If we use the accepted definition of autophagy to specifically mean "degradation of cytoplasmic contents," then very few, possibly no, viruses allow true autophagy to occur. Some viruses have evolved to inhibit autophagy because it is a threat, a way to clear cytosolic viruses and virus components from the cytosol. Most of these viruses, especially DNA viruses, actively repress autophagy initiation as infection progresses. Others prevent degradation by benefiting from specific aspects of the pathway. Many RNA

viruses use the autophagic machinery as a source of lipids and membranes providing scaffolds for RNA replication, vesicular refuges for capsid assembly and maturation cleavages, and trafficking vehicles for non-lytic exit of virus. This release mechanism involves release of the inner membrane vesicle, filled with virus, through fusion of the outer autophagosomal membrane with the plasma membrane. However, these viruses often inhibit acidification of autophagosomes, lysosome fusion, and even cargo loading. In some cases, the relationship of autophagy to a given virus changes depending on whether autophagy is induced before (anti-viral) or after (pro-viral) infection. Presumably this is because the pool of autophagic resources is limited, and pre-inducing autophagy depletes them and makes them unavailable to the virus, curbing virus replication.

The key questions to be answered in the next few years are:

1. Are there, in fact, any viruses that utilize degradative autophagy to promote their replication?

2. How are autophagy-specific proteins usurped by viruses, and why?

3. Are viral infections initiating the basal- or stress-induced autophagic pathways?

4. Is blocking cargo loading essential for virus production?

5. And finally, how do the released virus-containing vesicles, derived from autophagosome inner membranes, fuse with cells to initiate new infections?

Do-Hyung Kim

Signaling

Studies on the molecular mechanisms of macroautophagy/autophagy have been greatly advanced over the past decade with discoveries of key regulatory molecules and their signaling events. Despite the progress, we still cannot clearly explain the mechanisms that drive the dynamic membrane rearrangement during autophagy. It remains vague how post-translational modifications, interactions, and translocations of autophagy regulators are coordinated to trigger the nucleation, expansion, and closure of the autophagic membrane during autophagosome formation. To obtain clearer explanations of the long-sought-after mechanisms, we may need to decipher the coordinate regulatory relations that govern the spatiotemporal interplay between protein and lipid modifying enzymes, scaffolding proteins, membrane-binding proteins, and phospholipids. Important directions of study may also involve clarifying how autophagy is regulated in different cellular contexts via crosstalk with other signaling pathways, especially the pathways that regulate growth, death, and metabolism. The signaling mechanisms distinct between the canonical and the non-canonical autophagy pathways also remain as a key missing gap.

Daniel J. Klionsky

Other topics

There are currently 43 identified fungal *ATG* genes, with at least 3 more not yet published. In many cases, we still do not fully understand the function of those proteins or their mechanism of action. Further advances will likely involve

additional structural studies, in particular of subcomplexes, and looking at endogenous proteins. Regulation continues to be an important area of study. One issue is that autophagy plays an essential role in many aspects of cell physiology. Thus, it will not be possible to completely shut off the process in terms of modulating autophagy for therapeutic purposes; rather, controlling the regulatory network offers a more nuanced approach to fine tuning autophagy activity. Along these lines, a major challenge remains the demonstration that it is possible to manipulate autophagy for the purpose of improving human health. Autophagy has been implicated in a very wide array of diseases and in aging, but no one has yet shown that it is practical to modulate autophagy activity in a living person to prevent or ameliorate these conditions.

Nicholas Ktistakis

Membrane biogenesis and trafficking

One key question that is worth addressing concerns the source membrane used during selective macroautophagy/autophagy. I think there is a possibility that this may turn out to be distinct from nonselective autophagy, either because the amount of targeted cargo is limited and therefore the need for lipids to be incorporated into the forming autophagosome is not so large, or because the targeted cargo may also provide a membrane source if it happens to be itself a membrane-bound organelle (mitochondria, ER, lysosomes, etc.). However, it is also possible that a source membrane for all of these selective autophagy pathways is the ER, with ATG2 and ATG9 providing the route for lipid transfer and incorporation as is mostly the case for nonselective autophagy. A second key question concerns the role of liquid-liquid phase separated regions during autophagy induction. So far, SQSTM1 and RB1CC1/FIP200 have been found in such regions but it is likely that the list will expand. Why is it necessary to have such regions, what do they contain and what do they exclude, and how do they integrate with the downstream steps of autophagosome formation, induction and nucleation?

Marta Margeta

Neuroscience

In 2006, a couple of seminal papers conclusively demonstrated that disruption of basal macroautophagy/autophagy in the brain leads to neurodegeneration and accumulation of protein aggregates. In 16 years since that important discovery, there has been a lot of work to elucidate the role of autophagy impairment in the pathogenesis of neurodegenerative diseases and other neurological and psychiatric disorders, and much progress has been made across the board; however, many important questions remain unanswered. Here are some of them:

1. Both CNS and PNS are complex mixtures of cell types, with neurons (and their axons) only a single, albeit very important, cellular component; however, most autophagy research to date has been highly neurocentric. We need to learn a lot more about the physiological role and regulation of autophagy in all types of glial cells (astrocytes, oligodendrocytes, and Schwann cells in addition to microglia) as well as

pericytes, which together with astrocytes and endothelial cells form the blood-brain and blood-nerve barriers. We also need to broadly investigate the role of non-neuronal autophagy in the pathogenesis of various CNS and PNS disease processes.

2. Recent work has demonstrated that autophagy is important for synapse maintenance, but a lot remains to be learned in this key domain of neuroscience. To what extent is autophagy regulated by neuronal activity, and is this regulation limited to neurons or does it also involve non-neuronal cell types? What is the exact role of autophagy in synaptic plasticity and synaptic pruning? How do autophagic defects in these synaptic processes contribute to developmental and psychiatric disorders such as autism and schizophrenia?

3. How are autophagic mechanisms altered across the lifespan? There has been a lot of interest in how autophagy changes with aging, but due to technical limitations the advances in this field have been relatively modest; the pace of discovery should accelerate now that better in vivo autophagy monitoring tools have become available. We also need to establish whether autophagy is altered at other key developmental time points (such as early postnatal development, puberty, and adolescence) when the brain undergoes major restructuring and is particularly vulnerable to emergence of various neuropsychiatric disorders. What is the exact role of autophagy during different stages of neurodevelopment?

4. A key but poorly understood facet of many CNS diseases is that different neuronal populations are not equally susceptible to injurious stimuli; even in the setting of a relatively well-understood external insult, injury is typically restricted to just a few neuronal subtypes, and the patterns of selective neuronal vulnerability depend on the specific disease. (For example, pyramidal neurons in the CA1 sector of the hippocampus and Purkinje neurons in the cerebellar cortex are particularly susceptible to hypoxic/ischemic injury, while dopaminergic neurons of the substantia nigra are highly vulnerable to mitochondrial dysfunction.) While the mechanisms underlying selective neuronal vulnerability are almost certainly multifactorial as well as disease dependent, there is emerging evidence to suggest that differences in either baseline or induced autophagy are partly responsible. For example, it was shown that the ischemia-resistant neurons in the CA3 sector of the hippocampus induce autophagy in response to an ischemic insult, while the ischemia-sensitive neurons in the CA1 sector do not. Similarly, global deficiency of many a key autophagy protein selectively damages cerebellar Purkinje neurons, but it is not really understood how or why. These studies have only started to scratch a surface of this important scientific problem; we need to learn a lot more about differences in autophagy regulation across different neuronal populations, and the effects of these differences on selective vulnerability to different types of injury.

5. Last, but definitely not the least, the role of autophagy impairment in the pathogenesis of adult-onset neurodegenerative diseases needs to be further investigated, with Alzheimer disease (AD) emerging as a particularly complicated piece of the puzzle. On the one hand, brains of human AD patients show marked accumulation of autophagic vacuoles, reminiscent of autophagic buildup seen in genetic and toxic autophagic vacuolar myopathies. In addition, it was recently shown that a rise in autolysosomal pH is associated with Aβ accumulation within de-acidified neuronal autolysosomes in several AD mouse models. On the other hand, human genetic evidence supporting the role of autophagy dysfunction in the pathogenesis of AD is relatively weak: while genetic variants in a few proteins involved in the late stages of autophagy (such as BIN1 and PLD3 [phopholipase D family member 3]) raise the risk of late-onset AD, Mendelian disorders that affect the autophagy-lysosome degradation pathway have been linked to several other adult-onset neurodegenerative diseases (Parkinson disease, amyotrophic lateral sclerosis, and/or frontotemporal dementia) but not to AD. Moreover, genetic alterations that cause human disease by altering lysosomal acidification (such as mutations in VMA21, an essential assembly chaperone of the vacuolar ATPase, which cause autophagic vacuolar myopathy) are not known to increase the risk of either early or late-onset AD, although there is some evidence that PSEN1 (presenilin 1) mutations (which cause early-onset AD) raise lysosomal pH through their effect on V-ATPase assembly. These discrepancies likely reflect the complexity of the CNS and many of the unanswered questions listed above and will need to be clarified before any autophagy-modifying therapeutic approaches can be considered for either AD or other neurodegenerative diseases.

Christian Münz

Immunology

The molecular machinery of macroautophagy/autophagy is involved in many aspects of immune responses, including elimination of intracellular pathogens, limiting inflammation, antigen processing for MHC presentation and survival of memory immune cells. Challenges in this field are dissecting which of these functions are fulfilled by canonical autophagy versus non-canonical pathways that utilize components of the autophagy machinery, such as LC3-associated phagocytosis and ATG-supported exocytosis. Furthermore, the autophagy machinery plays both beneficial and detrimental roles for different arms and stages of immune responses, such as restricting MHC class I but favoring MHC class II antigen presentation and restricting inflammation but favoring intracellular pathogen degradation. Therefore, it will be important to identify interventions and the conditions under which to apply them to augment immunity to infectious disease agents and tumors, as well as to curb autoimmunity and other immune pathologies.

Morten Petersen

Plants

A key question is to address how tissue-specific macroautophagy/autophagy contributes to plant development, and biotic and abiotic stress tolerance, and how this is coordinated at the organismal level. Autophagy has been implicated in many aspects of plant development and stress tolerance; however, we have mostly based our knowledge upon the characterization of autophagy-deficient plants. Perhaps not surprisingly, homeostatic perturbations due to the life-long loss of autophagic activity can obscure the role of this process in many

aspects of plant development. Thus, conditional and/or tissue-specific knockout mutants may help to discriminate better between direct and indirect consequences of autophagic deficiencies.

We also do not know much about how different hormonal signals trigger autophagy. Is it via a common denominator or via specific components from separate signaling pathways? Another key question is therefore how do different signaling pathways employ autophagy to mediate both temporary and somatic reprogramming?

In addition to these two questions, we should also ask how to modulate autophagic activity to improve plant fitness. For example, as observed in animals, increased autophagic activity also improves plant performance. During the age of climate change autophagic activity thus represents an obvious target for agronomic intervention.

Junichi Sadoshima

Cardiovascular

Publications in the cardiovascular sector should clearly demonstrate novel molecular mechanisms and their functional significance in cardiovascular pathophysiology. In particular, addressing the cell type-specific roles of macroautophagy/autophagy in mediating the pathophysiology of the cardiovascular system is becoming increasingly important. The heart and blood vessels consist of many cell types, including cardiomyocytes, smooth muscle cells, endothelial cells, fibroblasts, inflammatory cells, etc., and the roles of autophagy and its underlying mechanisms in each cell type are quite diverse. In addition, autophagy in a particular cell type both affects the survival and death of the cell itself and influences organ physiology through autocrine/paracrine and inflammatory mechanisms [19]. A knowledge gap exists with regard to how autophagy and mitophagy in one cell type affect the function of other cell types. Another area of increasing importance is the study of lifestyle and dietary interventions. Investigating the involvement of autophagy and mitophagy in their salutary actions in the cardiovascular system and the underlying molecular mechanisms responsible for their effects is of great interest [20]. Finally, there is still a need for more studies addressing how basic science findings are translated to the bedside.

Isabelle Vergne

Bacterial infection

Over the past two decades, the key role of host macroautophagy/autophagy-related pathways in bacterial infection has clearly been demonstrated for a wide array of bacterial species [21]. In some cases, these pathways allow the elimination of the bacteria, whereas in others, they are manipulated by the pathogens to thrive inside the host. Although several cellular mechanisms, bacterial and host factors have been identified and characterized, our current understanding of the interplay between pathogenic bacteria and autophagy remains largely incomplete. Here, I would like to highlight two outstanding questions in the field of autophagy and bacterial infection:

1. Besides the bacteria itself, what is the full spectrum of autophagic molecular cargos during bacterial infections?

Mostly hypothesis-driven approaches have hitherto been applied to identify such cargos. A systematic approach such as proximity proteomics of autophagy receptors and LC3 proteins, combined with organelle enrichment [22], could bring important insights into the identity of these cargos and, thus, could potentially lead to the discovery of a new function(s) of autophagy during bacterial infection.

2. Do autophagy-related pathways play a role in bacterial infection in humans? The vast majority of studies have been performed, in vitro, in 2D human cellular models. Animal models of infection, including mouse and zebrafish, have been and continue to be instrumental in visualizing autophagy and exploring its role in vivo; however, only conserved molecular mechanisms and infection processes can be investigated. In the future, the combination of patients and human 3D organoids studies will definitely improve our understanding of autophagy in bacterial infection and its relevance as a target for host-directed therapy [23].

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References

[1] Amaravadi RK, Kimmelman AC, Debnath J. Targeting autophagy in cancer: recent advances and future directions. Cancer Discov. 2019 Sep;9(9):1167–1181.

[2] Liu J, Debnath J. The evolving, multifaceted roles of autophagy in cancer. Adv Cancer Res. 2016;130:1–53.

[3] Towers CG, Fitzwalter BE, Regan D, et al. Cancer cells upregulate NRF2 signaling to adapt to autophagy inhibition. Dev Cell. 2019 Sep 23;50(6):690–703 e6.

[4] Marsh T, Tolani B, Debnath J. The pleiotropic functions of autophagy in metastasis. J Cell Sci. 2021 Jan 22;134(2). DOI:10.1242/jcs.247056.

[5] Xia H, Green DR, Zou W. Autophagy in tumour immunity and therapy. Nat Rev Cancer. 2021 May;21(5):281–297.

[6] Kitada M, Koya D. Autophagy in metabolic disease and ageing. Nat Rev Endocrinol. 2021 Nov;17(11):647–661.

[7] Qian H, Chao X, Williams J, et al. Autophagy in liver diseases: a review. Mol Aspects Med. 2021 Dec;82:100973.

[8] Rabinowitz JD, White E. Autophagy and metabolism. Science. 2010 Dec 3;330(6009):1344–1348.

[9] Galluzzi L, Bravo-San Pedro JM, Levine B, et al. Pharmacological modulation of autophagy: therapeutic potential and persisting obstacles. Nat Rev Drug Discov. 2017 Jul;16(7):487–511.

[10] White E. The role for autophagy in cancer. J Clin Invest. 2015 Jan;125(1):42–46.

[11] Li Y, Chao X, Yang L, et al. Impaired fasting-induced adaptive lipid droplet biogenesis in liver-specific atg5-deficient mouse liver is mediated by persistent nuclear factor-like 2 activation. Am J Pathol. 2018 Aug;188(8):1833–1846.

[12] Ni HM, Woolbright BL, Williams J, et al. Nrf2 promotes the development of fibrosis and tumorigenesis in mice with defective hepatic autophagy. J Hepatol. 2014 Sep;61(3):617–625.

[13] Singh R, Kaushik S, Wang Y, et al. Autophagy regulates lipid metabolism. Nature. 2009 Apr 30;458(7242):1131–1135.

[14] Takamura A, Komatsu M, Hara T, et al. Autophagy-deficient mice develop multiple liver tumors. Genes Dev. 2011 Apr 15;25(8):795–800.

[15] Hernandez-Gea V, Ghiassi-Nejad Z, Rozenfeld R, et al. Autophagy releases lipid that promotes fibrogenesis by activated hepatic stellate cells in mice and in human tissues. Gastroenterology. 2012 Apr;142(4):938–946.

[16] Thoen LF, Guimaraes EL, Dolle L, et al. A role for autophagy during hepatic stellate cell activation. J Hepatol. 2011 Dec;55 (6):1353–1360.

[17] Castillo-Armengol J, Fajas L, Lopez-Mejia IC. Inter-organ communication: a gatekeeper for metabolic health. EMBO Rep. 2019 Sep;20(9):e47903.

[18] Ponpuak M, Mandell MA, Kimura T, et al. Secretory autophagy. Curr Opin Cell Biol. 2015 Aug;35:106–116.

[19] Nussenzweig SC, Verma S, Finkel T. The role of autophagy in vascular biology. Circ Res. 2015 Jan 30;116(3):480–488.

[20] Rabinovich-Nikitin I, Rasouli M, Reitz CJ, et al. Mitochondrial autophagy and cell survival is regulated by the circadian Clock gene in cardiac myocytes during ischemic stress. Autophagy. 2021 Nov;17(11):3794–3812.

[21] Keller MD, Torres VJ, Cadwell K. Autophagy and microbial pathogenesis. Cell Death Differ. 2020 Mar;27(3):872–886.

[22] Zellner S, Schifferer M, Behrends C. Systematically defining selective autophagy receptor-specific cargo using autophagosome content profiling. Mol Cell. 2021 Mar 18;81(6):1337–1354 e8.

[23] Lopez-Jimenez AT, Mostowy S. Emerging technologies and infection models in cellular microbiology. Nat Commun. 2021 Nov 19;12(1):6764.