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EDITORIAL

Autophagy participates in, well, just about everything

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Two years ago, I was asked to give a talk about autophagy and cancer. That seemed reasonable enough, but as a researcher who works primarily with yeast, I needed to do some extensive reading of the literature. Sure, I knew, or thought I knew, the basics about this topic, but this talk was for students, who might assume that what I said was actually correct, so I wanted to get it right. Yet, the more I read about the subject the less clear it became. The problem was not with any individual study, but rather trying to figure out what the overall "take home" message might be. One problem has to do with the fact that cancer studies generally are not carried out using yeast, and more's the pity. Although there are indeed different yeast strains, they are still fairly similar, at least compared with the differences inherent in other model systems. With cancer studies, for example, people use all sorts of cell lines. For those of us who are not well versed in mammalian cell lines, it can be difficult to sort out the relevance or to make comparisons. Add to this the fact that researchers are studying various types of cancer, and you have a real problem on your hands. The final complication when it comes to having a clear understanding of autophagy and cancer? Not all of these studies agree with one another.

So, what could I do for my talk? My first solution was to extend the topic from autophagy and cancer to autophagy and disease. Now, you may think that broadening the coverage to all diseases would only make that situation worse. However, this way I could pick and choose. I still decided to cover the highlights of autophagy and cancer, although that is not an easy task in and of itself—do you have any idea how many papers have already been published on this topic? Let's just say quite a few. One point I did take away from my reading, which I am sure you are already familiar with, is that the relationship between autophagy and cancer is complex. Thus, from a clinical perspective, the decision as to whether to inhibit or stimulate autophagy to augment an anticancer treatment depends on the type of cancer and its stage of progression. During my talk, this allowed me to emphasize the importance of understanding how autophagy is regulated (after all, no reason not to get in a little promotion for my own research interests). I concluded my discussion of cancer by noting that there were certainly controversies in this field, which means that more research is needed.

Then, on to other diseases. I have to say that one of the issues I encountered in my reading is that, despite all of the research, in many cases the molecular mechanism relating autophagy to a particular disease may not be known. This is not stated as a criticism, simply as a fact. I mean that it would have been neat to be able to present all these examples of how and why autophagic dysfunction contributes to a disease, but we do not always know the answer. That should not be surprising considering that the molecular analysis of autophagy is still in its infancy. Nonetheless, for my purposes I tried to focus on diseases where something was known about the molecular basis relative to autophagy. This still provides a wide range of options where there are clear mechanistic connections such as for some aspects of xenophagy as part of the immune response, and mitophagy with regard to its role in neurodegeneration. But, how about heart disease? Lung disease? Liver disease? Macular degeneration? Diabetes? Kidney disease? Myopathies? Whoa.

At this point, you may be wondering about the "take home" message of this introduction. That is quite simple. The topic of autophagy is huge. Whether you are interested in autophagic dysfunction and its relation to disease, or the role of autophagy in normal physiological processes, there are some issues you need to deal with: (1) There is often a vast literature—the "explosion" of research in the field of autophagy has led to a corresponding number of papers. (2) The field is rapidly evolving, making it difficult to keep up. (3) As a result of items 1 and 2, there are many uncertainties

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and conflicting data. But, because we are so nice, and have your best interests at heart, here we present a collection of chapters on key topics in the autophagy field. Each chapter is, of course, prepared by experts with the goal of helping you sort out the critical points that you need to know, and making it clear as to the current state of the relevant research.

After a general introductory chapter on "Autophagy and disease: unanswered questions" [1] we present a chapter by Allen and Baehrecke that focuses on "Autophagy in animal development" [2]. Here, we can learn about some of the functions carried out by a properly working autophagy pathway. One striking point is that autophagy is important at essentially every stage of normal organismal development, participating in the removal of paternal mitochondria following fertilization, during embryogenesis, and immediately after birth with subsequent roles throughout life, particularly for cells under various stress conditions. This chapter also provides an overview of the wide range of model systems that are used to study autophagy, and some of the roles of this process outside the realm of humans, including tissue regeneration.

Cadwell and colleagues present a thorough introduction to the role of autophagy as it pertains to host–microbe interactions [3]. This chapter points out the molecular pathway involving autophagy receptors and upstream regulatory proteins that allow for intracellular microbes to be sensed and eliminated. Additional important points concern the mechanism through which autophagy acts to modulate the inflammatory response so that we do not overreact to an infection, and the fact that some processes (such as LC3-associated phagocytosis and secretory autophagy) depend on a subset of autophagy-related proteins. Along with bacteria, the chapter on "Autophagy and microbial pathogenesis" considers other microbes including viruses and protists.

Hübner and Dikic follow with a chapter that focuses on "ER-phagy and human diseases" [4]. ER-phagy or reticulophagy, provides another example where substantial information is available concerning the molecular mechanism. As with all organelles in most cell types, removal usually needs to be carefully controlled to avoid cell death. In the case of the endoplasmic reticulum, several receptors have been identified for the selective removal of parts of this organelle. This chapter provides an overview of our current understanding of these receptors, and the consequences with regard to human disease when the process goes awry.

Autophagy and autophagy-related proteins play multiple roles in the immune response, directly fighting off invasive microbes, secreting cytokines, and participating in antigen presentation. Fimia and colleagues discuss the function of the TRIM family of E3 ubiquitin ligases with an emphasis on their role in innate immunity [5]. The TRIM proteins act at several steps of the process. Some of these proteins affect autophagy induction through their action on the ULK1 and BECN1-containing class III phosphatidylinositol 3-kinase complexes. Others act to inhibit or activate autophagy by mediating the downregulation of AMPK or MTOR. Still others have a transcriptional role. Furthermore, the TRIM proteins function in multiple ways, in some cases directing ubiquitination of target proteins for downregulation, but for others acting as scaffolds for complex assembly.

Finally, we come full circle with a chapter by Levy and Thorburn that discusses in detail the complex interactions between autophagy and cancer [6]. In addition, these authors consider the therapeutic implications of autophagy modulation, the effectiveness of current treatment regimens, and possible future options. This chapter also deals with the connection between autophagy and apoptosis as it relates to cancer therapy.

Certainly, we could include many additional chapters on a wide range of topics. This series is not meant to be comprehensive or exhaustive. In fact, the field is still moving too rapidly to expect any single series of papers to provide a definitive discussion of the many roles of autophagy in health and disease. Nonetheless, it is critical that we periodically step back and assess the current state of knowledge, which can be extremely helpful in determining the direction of future research. In that regard, we hope that you find this set of chapters both informative and useful.

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