

Preface

This book was inspired by a stream of nearly simultaneous reports in 2004 and 2005 demonstrating that the fundamental biological process of autophagy, primarily known for its role in cytoplasmic maintenance, represents a previously unrecognized innate and adaptive immunity mechanism that functions as a defense against intracellular pathogens and probably has other roles within the immune system. Although hints to the role of autophagy in immune defenses and other roles in immunity have existed in the literature, the most recent burst of publications made a compelling and definitive case for the importance of autophagy in immunity. A further motivation for this project came from the opportunity to merge these new findings with the superb recent progress on genetics, biochemistry and cell biology of autophagy. The product is a book covering the basic aspects of autophagy as a cytoplasmic maintenance process playing a role in cell survival and death, its role in health and disease in general, and the new cutting edge – the role of autophagy in immunity. Using this book, the reader can find a full range of information on autophagy in one place covering both its fundamental molecular mechanisms and its many physiological roles.

Autophagy is a homeostatic intracellular mechanism, whereby a cell digests parts of its own cytoplasm for removal or turn-over, as eloquently summarized in the Foreword by P. Seglen. The term autophagy represents a set of distinct yet related pathways. These range from the robust process of macroautophagy to a rather subtle process of chaperone mediated autophagy, as detailed in Chapter 1 by J. Legakis and D. Klionsky, which also provides the fundamentals of autophagy based on the powerful genetics in yeast and other organisms. Macroautophagy sequesters significant portions of the cytosol or whole organelles into a characteristic double membrane vacuole termed the autophagosome, for eventual degradation in autolysosomes, covered extensively in Chapter 2 by S. Tooze and colleagues and Chapter 3 by N. Mizushima. Chaperone mediated autophagy, covered in some detail in Chapter 4 by A. Cuervo and colleagues and touched upon in Chapter 12 by D. Schmid and C. Münz, is a degradative pathway whereby individual proteins are imported directly into the lysosomes. In macroautophagy, or its variant manifestation of microautophagy, the trapped cytosol or organelles are eventually delivered to degradative compartments (in mammalian cells – autolysosome) for digestion and removal. In its probably

most common presentation, autophagy recycles stable cytosolic macromolecules, such as proteins with long half-lives, to supply nutrients and maintain essential cellular anabolic needs and viability under starvation conditions. The organelle removal function of autophagy is a just as important housekeeping function, by controlling the pool of peroxisomes or removing compromised mitochondria, in the latter case potentially protecting cells from unscheduled apoptosis. Although autophagy is a cell maintenance mechanism, under certain conditions, excessive autophagy can cause non-apoptotic programmed cell death, covered in Chapter 5 by Y. Debnath and C. Fung. Autophagy has been implicated in cancer, degenerative disorders, such as Huntington, Parkinson, and Alzheimer diseases, normal development, and aging, covered in detail in Chapter 4 by A. Cuervo and colleagues.

A number of very precise studies on anti-viral action of autophagy have been the true forerunner of our present more general understanding of the role of autophagy in defense against intracellular pathogens, as covered in Chapter 13 by B. Levine. More recent studies demonstrate that autophagy is also an innate immunity effector against intracellular bacteria, a central theme of the second half of this book, encompassing: Chapter 6 on *Mycobacterium tuberculosis* elimination by autophagy (Harris et al.); Chapter 7 by T. Yoshimori and A. Amano on autophagic elimination of streptococci if they invade host cells and find themselves in the cytosol; Chapter 8 on the role of autophagy in capturing the intracellular *Shigella* and its ability to escape this process; and Chapter 9 by K. Rich and P. Webster on *Listeria*. Some highly evolved pathogens have mechanisms for harnessing autophagy to their own benefit, as suggested in Chapter 10 by M. Gutierrez and M. Colombo and discussed in Chapter 11 by M.-P. Stein and C. Roy. The duality of effects of autophagy is also reflected in the Addendum to B. Levine's Chapter 13 provided by J. Sparks and M. Denison. Significantly, autophagy has a strong impact on MHCII presentation (Chapter 12 by D. Schmid and C. Münz) and is controlled by cytokines (Chapters 6 and 13) clearly extending the role of autophagy to adaptive immunity.

The goal of this volume was to provide the reader not only with the applications of autophagy in infectious diseases and immunity, but also to generate a definitive text for autophagy in general. In other words, a reader who is interested primarily in the fundamental principles and broad biological aspects of autophagy, should find this book an indispensable companion and a comprehensive source of information. For those who are primarily interested in the burgeoning field of autophagy in innate and adaptive immunity, the chapters covering the basic principles of autophagy are just as important to understand fully the underlying processes.

The book starts with a foreword by Professor Per Seglen, a doyen in the field of autophagy, who has defined many biochemical and cell biological features of autophagy and has also produced both classical and contemporary highly cited papers in this field. A careful reader of the foreword will extract many useful concepts on autophagosomes, amphisomes and autolysosomes, and precious cautionary notes on interpretations of cause and effect in diseases and in cell

survival vs. cell-death promoting faces of autophagy. The editor is indebted to Per for his willingness to write a foreword to this volume and give the reader both his sage advice on general aspects of autophagy and sum it all up including the latest developments in the context of defense against intracellular pathogens.

Furthermore, the reader is a true beneficiary of the combination of excitement and enthusiasm that pervades the field of autophagy research, and enormous expertise of the contributing authors in this area. The editor of this book is indebted immensely to all contributing authors. The chapters by Drs. Ana Maria Cuervo, Daniel Klionsky, Beth Levine, Sharon Tooze and Naboru Mizushima, taken together, can give a textbook on autophagy as a standalone product. Likewise, the chapters that link autophagy with innate and adaptive immunity by Drs. Christian Münz, Chichiro Sasakawa, Tamotsu Yoshimori, and others summarize the new breakthroughs in immunological applications of autophagy. They also define the nidus for the developing field of immunophagy, a term used by the Editor of this book in a recent review in *Current Opinion in Immunology* to describe collectively these processes.

I acknowledge the excellent coordination and open lines of communication with the publisher including the gentle prompts from Andreas Sendtko, importance of NIH funding (AI45148 and AI42999) for all my scientific activities including this one, great support and understanding at home beyond what a person can expect or deserves, and above all the collective responsiveness and enthusiasm for this book by the main protagonists in the field of autophagy. My great personal and professional respect for many of the contributors to this book has been reaffirmed in the process.

Placitas (between Albuquerque and Santa Fe), April 2006

Vojo Deretic