Preface

Autophagy is a fundamental biological process that enables cells to adjust cytoplasmic mass, quality and organization through capture and autodigestion of their cytoplasmic components. Autophagic targets range in size and complexity from individual long-lived macromolecules to whole organelles and microbial invaders. The principal role of this ubiquitous eukaryotic homeostatic mechanism is to ensure cell survival under adverse conditions, including nutrient absence, growth factor withdrawal, accumulation of toxic protein aggregates, and faulty organelles (e.g., leaky mitochondria), or infection by intracellular pathogens. The physiologic and pathophysiologic roles of autophagy (and defects in autophagy) are vast, encompassing cancer, neurodegeneration, metabolic diseases, aging, and (as of more recently) immunity. The immunological roles of autophagy fall into two broad categories, including: (1) effects on the control of general homeostasis in immune cells that parallel its roles in other cell types in the body, and; (2) effects on specialized functions of immune cells or other cellular targets of infection that enable the host to effectively deal with microbes or microbial products.

In this volume, experts in autophagy provide overviews and more detailed dissections of the basic molecular and cellular mechanisms of autophagy (chapter by Yang and Klionsky), the signaling cascades that control these processes (chapter by Codogno and colleagues), and the fundamental and applied physiological roles of autophagy (chapter by Mizushima). The role of autophagy in cellular homeostasis as it relates to immunity is covered in two chapters; Pua and He describe the role of autophagy in lymphocyte homeostasis and Espert and Biard-Piechaczyk describe the effects of HIV on lymphocyte cell death through autophagy. These chapters provide contrasting examples of how autophagy can be used to normally adjust lymphocyte populations or be misdirected by a potent virus to deplete certain types of immune cells. A similar theme of “pros and co s” is seen in the chapters that comprise the bulk of this volume, covering what is likely to be the most ancient specialized immune function of autophagy: the direct elimination of intracellular microbes. In the chapters by Orvedahl and Levine, Deretic and colleagues, Huang and Brumell, Yoshimori and Amano, and Sabauste, autophagy is revealed in its primordial immune form of an innate, cell-autonomous defense against the microbes that manage to erode into or specifically invade the interior of the eukaryotic cell. The chapters by Kirkegaard, Orvedahl and Levine, and Campoy and Colombo

reveal the flip side of these relationships, addressing specialized adaptations that successful intracellular pathogens have evolved to deal with autophagy as an antimicrobial mechanism. Moreover, the broad role of autophagy as a cell-autonomous innate immunity mechanism that is deeply engrained in the eukaryotic cell is evidenced by its role in plants, as discussed in the chapter by Dinesh-Kumar and colleagues. Lastly, the chapters by Tal and Iwasaki, Gannagé and Münz, and Virgin and colleagues cover some of the most intriguing immunological applications of autophagy, including: (1) the ability of autophagosomes to capture cytosolic microbial products for presentation to the lumenally-oriented innate immunity receptors such as Toll-like receptors (Tal and Iwasaki), thus activating innate immunity; (2) a similar topological inversion function of autophagy in antigen presentation, whereby microbial antigens expressed in the cytosol of the host cell can be processed and loaded onto lumen-facing MHC II molecules for proper presentation to T cells (Gannagé and Münz), thereby functioning in adaptive immunity as well as in thymic T-cell selection; and (3) the role of autophagy genes as their function relates to specialized aspects of highly differentiated cells in the context of understanding inflammatory disorders such as Crohn's disease (Virgin and colleagues).

The chapters in the book describe an increasingly complex set of interactions that are beginning to be unraveled between the autophagy pathway, infectious diseases, and immunity. In its most primal form, autophagy may be a universal defense mechanism by which individual eukaryotic cells (or unicellular organisms) protect themselves in a cell-autonomous fashion by "eating" the microbes that attack them. With the evolution of metazoan organisms, the autophagy pathway has likely been utilized to enable such organisms to develop a more complex immune system. Not only is autophagy a primordial defense mechanism, it is also a pathway that shapes the dynamics of immune cell populations, that contributes to immunological tolerance and the control of inflammation, and that links pathogen recognition to the activation of innate and adaptive immunity. And—based upon the pace of new discoveries in this area—this list may just be the tip of the iceberg. Hopefully, this volume of *Current Topics in Microbiology and Immunology* will stimulate investigators to delve even deeper into this exciting field.

Dallas, TX, USA — Beth Levine
Osaka, Japan — Tamotsu Yoshimori
Albuquerque, NM, USA — Vojo Deretic

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