Preface

IMMUNORECEPTOR SIGNALING AS A TOPIC OF RESEARCH has a history of about 30 years. Though the effects of plant lectins on lymphocyte activation were studied back in the 1960s, the modern era began once the lymphocyte antigen receptors were isolated and characterized. After a number of false starts, the T-cell antigen receptor (TCR) was finally identified and its multi-subunit character described in the 1980s. Though surface immunoglobulin was well known to be the recognition component of the B-cell antigen receptor (BCR), the signaling components of this receptor as well as the family of Fc receptors were also identified during this period.

Since then and with the involvement of increasing numbers of researchers, the field has expanded and has flourished due to the power of modern multidisciplinary research. Cellular immunology approaches demonstrated how receptor engagement affects lymphocyte activation, cytokine production, and elaboration of cell-surface molecules. Biochemical approaches not only resulted in isolation of the receptors but also an increasing list of downstream signaling molecules. The latter include protein tyrosine and serine kinases as well as a growing list of their substrates, all central to immunoreceptor signaling. The analysis of complexes of signaling molecules and the protein–protein interactions that make up these complexes remains an active area of research.

The molecular biology revolution that affected all of biomedical research over the same timespan also helped to transform immunoreceptor signaling research. Modern molecular biological tools allowed for the identification and characterization of the receptors and downstream signaling molecules. Genetic approaches such as the generation of mutants and their expression then allowed for the role of these molecules to be defined in cells and in engineered mice. Recently, the application of cell biologic and modern imaging techniques has triggered a new wave of discoveries. The application of these methods led to the discovery of synapses formed during cell–cell contact that are involved in signaling. Microscopic studies now track interactions of single signaling molecules within cells in real time. With the increasing acquisition of large quantities of data, computational approaches are being used to help understand the complexity of these signaling pathways.

Our hope here is to familiarize the reader with the latest discoveries in this field. We also hope that they convey a sense of the excitement about the incredible progress achieved over the last 20 years. The chapters cover a wide range of topics and, in aggregate, our hope is that they provide a comprehensive sense of the current state of the field.

We begin with discussion of TCR and BCR structure and function. Downstream of both of these receptors and receptors of the innate immune system, discussed next, are the protein tyrosine kinases (PTKs) of the Syk family. We continue with a chapter reviewing one of these PTKs, the central TCR-coupled kinase, ZAP-70, followed by chapters focusing on two of the proximal substrates of this kinase, LAT and SLP-76. Both chapters cover the topic of protein–protein interactions and signaling complexes. Members of the Tec family of PTKs, which are also activated following immunoreceptor engagement and are in turn responsible for activation of a variety of signaling enzymes, are the subject of the next chapter.

Engagement of antigen or immunoglobulin receptors alone does not result in full cellular activation. A number of additional receptors are required and this topic is reviewed in chapters on CD28 co-stimulation and the SLAM and SAP families of molecules. The activation of immunoreceptors leads to the activation of serine kinases and changes in lipid metabolism and ultimately in activation of transcription factors such as NF-κB, as well as to changes in the cytoskeleton; chapters on these

topics follow. We conclude with two chapters with a more global perspective. The first describes formation of the immune synapse of activated lymphocytes. Many of the molecules reviewed in the preceding chapters localize to this structure. The final chapter brings a systems approach to the study of the immense complexity of immunoreceptor signaling.

We hope that this collection brings together many of the major topics and approaches in this field. Perhaps this overview will aid in stimulating the next many years of fruitful research. We very much appreciate the efforts of several individuals at Cold Spring Harbor Laboratory Press. Richard Sever initiated the project and provided enthusiastic support for it. Kaaren Kockenmeister supervised production of the chapters and Joan Ebert guided and prodded editors and authors alike. Finally, we are grateful to our colleagues whose work has led the field and whose authorship is responsible for *any* success of this volume.

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