Preface

The NF-κB pathway brought mammalian signal transduction into the modern era, allowing the analysis of cell signaling to become inclusive and holistic. Prior to its definition, biologists had focused on receptor-proximal events, largely through study of receptor tyrosine kinases and G-protein-coupled receptors or the study of isolated protein kinases. The gaping hole in our understanding at that point was the connection to the nucleus. It was clear that many of the physiological effects of receptor signaling were achieved by altering gene expression, but how signals were transduced from the plasma membrane to the nucleus was by-and-large a mystery. The elucidation of NF-κB signaling in all of its molecular glory provided a new paradigm for understanding how receptor signaling can elicit transcriptional responses in mammalian cells. Even more importantly, NF-κB helped transform the study of cell signaling from dealing with cultured cells to consideration of whole animal systems.

As David Baltimore points out in his introduction, NF-κB was born rather innocently in a search for transcriptional regulators of the immunoglobulin locus. At the time, this effort was directed towards understanding the orchestrated changes in gene expression that take place during lymphocyte development. However, by following their noses, scientists in the Baltimore lab soon realized that the nuclear accumulation of the NF-κB DNA binding proteins could be induced by a number of extracellular stimuli and set out to understand how this molecular connection was made. The discovery that NF-κB exists in a latent form in the cytoplasm and translocates to the nucleus in response to various stimuli changed the way mammalian signal transduction was conceptualized.

What followed was a breathtaking explosion of research that uncovered pivotal roles for NF-κB in a host of biological processes critical for normal physiology of animals and their ability to counter stress, disease, and infection. As Jules Hoffman discusses, NF-κB emerged early in animal evolution as an important regulator of development and as a defense mechanism against invading pathogens, themes that have been embellished in vertebrate evolution. Although mammals no longer count on NF-κB in the control of general development and morphogenesis, they use it to signal downstream of a host of receptors, many of which are members of extended gene families to control responses to stress, infection, and injury.

This collection includes reviews of the molecular mechanisms by which NF-κB transcription factors are activated and exert their function in the nucleus, as well as reviews that summarize certain realms of biology that are particularly influenced by NF-κB signaling. Ingrid Wertz and Vishva Dixit focus on the mechanisms whereby receptors that detect antigens, inflammatory cytokines, and foreign organisms utilize protein–protein interactions and the ubiquitin system to engage IkB kinase (IKK) to initiate NF-κB signaling. The structure of IKK complex components and the elaborate regulation of its protein kinase activity are described by Alain Israël in his contributon. Andrea Oeckinghaus and Sankar Ghosh summarize the process by which IkBs sequester NF-κB in a latent state in the cytoplasm and how IKK action relieves this inhibition. Yinon Ben-Neriah and colleagues discuss the role of ubiquitination in the regulated degradation of the IkBs. The Rel-homology DNA binding domains of NF-κB transcription factors are discussed in structural detail by Tom Huxford and Goury Ghosh. The various NF-κB heterodimers have distinct target genes, as discussed by Ranjan Sen and Steve Smale, and can be altered in their transcription regulatory activities by post-translational modifications and association with co-factors, as discussed by

Fengyi Wan and Mike Lenardo. Chromatin structure further shapes the transcriptional output of NF-κB dimers, as reviewed by Gioacchino Natoli. The overall biological output of NF-κB signaling must be viewed from a systems biology perspective, as argued by Ellen O'Dea and Alex Hoffmann, whereas Steve Gerondakis and Uli Siebenlist recount the manifold ways in which NF-κB signaling controls lymphocyte differentiation, activation, and function in vivo. Equally important is the regulation of innate immunity and inflammatory responses, as presented by both Toby Lawrence and Michael Karin. Inflammation can promote cancer development, and Michael Karin outlines the compelling evidence for the critical pathogenic role played by NF-κB signaling in this process. Not surprisingly, cancers of many varieties accumulate genetic lesions that subvert NF-κB signaling to protect against cell death and promote proliferation, offering many possible avenues for therapy, as discussed by Lou Staudt. Barbara and Christian Kaltschmidt remind us that without NF-κB in our neurons, we would suffer learning disabilities and memory loss and would gain little from reading collections like this!

Twenty-four years after the discovery of mammalian NF-κB and more than 25,000 publications later, there remain mysteries and challenges in the NF-κB field. The contribution by Tao Lu and George Stark demonstrates that unbiased genetic screens continue to yield new regulators of NF-κB, so it will be years before we have a complete parts list for this system and a full understanding of its working. Given the dysregulation of NF-κB in inflammatory and autoimmune diseases, as well as in cancer, it is imperative that precise methods to manipulate NF-κB are developed. This will be a challenge given the baroque regulation of the NF-κB signaling system and its diverse biological functions, but one that can be met by building on the strong edifice of knowledge presented in this volume.

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Michael Karin
University of California, San Diego

Louis M. Staudt
National Cancer Institute

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