EDITORIAL

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Celebrating 25 years of NF-κB

Few proteins have had as profound an influence on immunity and biology as the transcription factor NF-κB.

Systems analyses and bioinformatics metadata mining are commonly used today as state-of-the-art approaches for identifying nodal components, whether proteins, genes or regulatory pathways, that intersect to affect biological processes or influence phenotypes. This approach allows connections to be made where none are readily apparent. Twenty-five years ago, using a simple gel-electrophoresis mobility-shift assay, Ranjan Sen and David Baltimore identified a DNA-binding factor that has since been found to be ancient and evolutionarily conserved and to be linked to many biological pathways. It influences cellular development, innate and adaptive immune responses, the induction of inflammatory mediators and wound repair, and, when dysregulated, can lead to various forms of cancer, autoimmunity and chronic inflammatory syndromes. This factor is NF-κB.

The first paper, published in the journal *Cell* (**46**, 705–716 (1986)), reported the identification of DNA-binding activity in B lymphocytes that specifically recognizes an enhancer element found in the gene encoding the immunoglobulin-κ light chain. Shortly thereafter, Sen and Baltimore presented evidence that this activity is inducible and that its expression is not restricted to the B cell lineage (*Cell* **47**, 921–928 (1986)). This second paper is chock-full of hints about signaling pathways (activation by lipopolysaccharide and phorbol esters) and means of regulation (no requirement for *de novo* protein synthesis, which suggests the existence of preformed complexes in cells awaiting the proper stimulus) and the possibility that a labile repressor may govern the DNA-binding activity. Since then, the molecule responsible for this activity, known as nuclear factor-κB (NF-κB) but actually a family of five related Rel-family proteins, has emerged as the central orchestrator of inflammation and immune responses and has been shown to have a critical role in homeostasis of cells of the immune system by maintaining the expression of prosurvival genes. So far, over 35,000 articles have been published that involve some aspect of NF-κB biology. Many more are sure to follow.

This issue of *Nature Immunology* marks the seminal discovery of NF-κB by presenting a series of six specially commissioned reviews in the Focus on 25 Years of NF-κB (http://www.nature.com/ni/focus/NF-kB/index.html). In the focus overview, David Baltimore outlines five states associated with NF-κB biology: latency, induction, response, resolution and pathology. He also points out holes in the present state of knowledge—for example, how particular stimuli can trigger unique subsets of NF-κB target-gene expression, whereas other stimuli activate different sets of targets. Context is surely key, for the constellation of other factors induced in the cell at the time and for the duration of the signal; for the array of *cis*-recognition sites found in the regulatory regions of the target genes and the transcription factors that associate with these sites; and for the diversity of covalent modifications to NF-κB itself. Here, systems biology might provide hints about the 'logic' of the regulation of gene expression by NF-κB.

In a historical commentary, Ranjan Sen recounts the discovery of NF-κB during a search for factors that influence the recombination and transcription of immunoglobulin genes in cells of the B lineage. Elucidation of how the immunoglobulin gene enhancers function could provide insight into the regulatory mechanisms that govern gene activity. The trick was to break the problem down into smaller component parts to allow delineation of the enhancer sites through the use of restriction endonucleases and to determine which nuclear factors bind.

Steve Smale discusses the regulatory hierarchy that governs target-gene selection by NF-κB to ensure proper gene expression. In particular, he reviews the chromatin landscapes present in regulatory loci of NF-κB target genes and how the specificity of the response is governed by stimulus-induced chromatin remodeling. That is, the binding sites themselves must be made accessible before NF-κB, and associated partner proteins can activate or, in some cases, repress gene transcription.

Sankar Ghosh and colleagues review the multiple signaling pathways that activate NF-κB and how other signaling pathways intersect to influence the ensuing NF-κB response. Many factors seem to converge on NF-κB, and sorting out the mechanisms by which the specificity of the response is maintained is a daunting task. A commonality in the activation scheme is the ubiquitin-dependent assembly of multiprotein kinase complexes that inactivate the inhibitor IκB that tethers cytosolic NF-κB. These complexes are themselves subject to multiple layers of regulation by ubiquitin-editing enzymes. The exact nature of many of these complexes and the scenarios that drive their interaction remain a focus of ongoing research.

Jurgen Ruland discusses the mechanisms by which NF-κB signaling is terminated to prevent potential tissue pathology due to prolonged expression of inflammatory mediators. Because the response activated by NF-κB is so potent, tight regulation is needed. Fortunately, many of the NF-κB target genes encode inhibitors of the signaling pathways, which allow the inflamed tissues to reset to normal function, in a classic feedback-inhibition way, once the danger has passed.

Finally, Yinon Ben-Neriah and Michael Karin delve into the pathologies associated with NF-κB dysregulation. They discuss the way many cancers can arise after excessive activation of the innate immune response, a scenario in which wound-healing processes can evade normal tissue growth–control mechanisms. Notably, they point to the anti-inflammatory and antitumorigenic roles of NF-κB, as certain mutations in the gene encoding NF-κB or inhibition of NF-κB itself can lead to more severe disease in some settings.

Clearly, despite 25 years of research centered on NF-κB, much remains unknown. Further research will no doubt identify additional regulatory modules that either activate or repress NF-κB or its target genes. Gaining insight into these processes and understanding how they contribute to human health and disease should remain a top priority.