Introduction to a Special Issue on IFN Regulatory Factors in Innate Immune Responses

Keiko Ozato

THIS SPECIAL TOPIC issue assembles review articles from 6 laboratories where the interferon regulatory factors (IRFs) have been actively investigated in recent years. This issue covers newly revealed aspects of IRFs in viral infection and myeloid cell development, and discusses the relationship with endotoxin-induced inflammation. It also features IRFs' role in regulating cancer microenvironment formed by myeloid cells. In addition, it presents recent advancement on genome-wide occupancy of IRFs during development and upon pathogen stimulation, addressing the significance of enhancers that shape chromatin. Lastly, the issue examines a chromatin binding factor BRD4 that bridges IRFs and chromatin in transcription, and introduces possible therapeutic avenues to autoimmune and chronic inflammatory diseases as well as leukemia.

Below Is a Brief Synopsis of Each Review

Batistini and her associates have been studying the role of IRF family proteins in HIV infection for many years. This article summarizes the importance of this family of transcription factors in antiviral defense against retroviruses, and RNA and DNA viruses. It focuses on viral counterattack against host immunity showing that IRFs are a major target of viral attack, leading to abrogation of IFN and IFN-stimulated genes (ISGs). The article features increasingly complex mechanisms through which viruses undermine IRFs' activities.

The Tamura laboratory has been a consistent frontrunner in studying the role of IRFs in hematopoietic cell development and leukemogenesis. In this article, Kurotaki and Tamura hone in on the role of IRF8 in the development of myeloid lineage cells and offer the latest bird's eye view illustrating how this transcription factor directs development of the Ly6C⁺ macrophages, dendritic cells, and microglia. The authors also describe genome-wide IRF8 binding in developing myeloid cells and unveil extensive co-occupancy with PU.1. Their article extends to recent publications on IRF8–Batf3 interactions that affect dendritic cell subset development.

The Abrams laboratory recently published stimulating findings on myeloid-derived suppressor cells (MDSCs) and the role IRFs play in mammary cancer microenvironment. MDSCs suppress T-cell antitumor immunity, associated with poor prognosis in various tumors. Here Abrams and associates review derivation of MDSCs and its relationship with myeloid cell development. The authors conclude that downregulation of

IRF8 in a myeloid progenitor stage is a critical event in MDSC formation, for which STAT3/5 and Socs3 may be implicated.

The Vogel laboratory has been active in studying bacterial lipopolysaccharides (LPS)/endotoxin on macrophage activity. The article from this group features LPS-induced tolerance, in which inflammatory responses are silenced upon repeated stimuli. It discusses recent findings that this tolerance mediated the formation of repressive chromatin by the histone methyltransferase G9a. The article also describes the role of BRD4 in transcription of ISGs in relation to histone acetylation and mRNA elongation.

The Natoli laboratory has been leading in presenting genome-wide transcription factor occupancy and histone modifications in macrophages. The article in this series (Mancino and Natoli) examines genome-wide binding of IRFs (in particular IRF8) in macrophages, showing the importance of the pioneer transcription factor PU.1 in epigenetic setting of a macrophage chromatin landscape. It highlights a prominent shift in IRF8 genome occupancy upon stimulation. The article further points out the possibility that IRF8 itself (and IRF4, by inference) possesses a pioneer or like function.

The Ozato laboratory has been studying the role of IRFs in innate immunity and the mechanism of action in chromatin focusing on BRD4 and histone H3.3. This article from the Ozato laboratory attempts to extract, from the existing public database, histone modification landscapes in and around each of IRF genes in various human cells. The efforts found that functionally related IRFs (IRF1/IRF2, IRF3/IRF7, and IRF4/IRF8) share similar chromatin landscapes, inferring their transcriptional state, poised or constitutive expression, and hidden potentials. It also reviews the rapidly moving research on BRD4 and its small molecular inhibitors. It highlights that IRFs are a target of these drugs, which may offer a new strategy for controlling leukemia and chronic diseases.

Address correspondence to:

Dr. Keiko Ozato

Division of Developmental Biology

National Institute of Child Health and Human Development

National Institutes of Health

6 Center Drive

Bethesda, MD 20892

E-mail: ozatok@nih.gov