Interferons, Interferon Receptors, Signal Transducer and Transcriptional Activators, and Interferon Regulatory Factors*

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Interferon, the first cytokine discovered, was identified by Isaacs and Lindenmann (1) during their seminal studies 50 years ago on virus interference. They reported that influenza-virus infected chick cells produced a secreted factor that transferred a virus-resistant state to previously uninfected cells (1). Importantly the resistance was displayed against both the homologous inducing virus and heterologous viruses. The factor was designated interferon (IFN) because of its ability to interfere with virus growth (1). We now know considerable detail about the IFN system and its role in antiviral innate immunity (2). The biochemical mechanisms by which viral infection triggers the production of type I IFNs was the subject of a thematic series of minireviews that appeared in The Journal earlier this year (3–5). Extensive insight into our understanding of the biochemical mechanisms by which the type I interferons themselves signal to exert their biologic actions also has been gained. Four minireviews in this issue provide updates on the interferons, their receptors, and two families of transcription factors that broadly affect IFN system gene expression and immunity (6–9).

The principal features of the JAK-STAT signal transduction pathway by which interferons transcriptionally activate cellular gene expression are summarized in Fig. 1. Interferon proteins are historically characterized as type I (α, β) or viral IFNs and type II (γ) or immune IFN (2). The human type I family of IFNs now include additional members, for example IFNs ε, κ, and ω. Both type I and type II IFNs exert their actions through cognate receptor complexes, IFNAR and IFNGR respectively, present on cell surface membranes. Additionally, novel interleukin 10-related cytokines, now known as type III IFN or IFN-λ, display activities and functions much like the type I IFNs, although the type III IFN-λ proteins utilize a different receptor complex to signal. IFN receptor-mediated signaling leads to the activation of latent cytoplasmic factors, the signal transducers and activators of transcription (STAT) family of proteins, which are activated by a process that involves members of the Janus tyrosine kinase (JAK) family (Fig. 1). STATs, together with members of the interferon regulatory factor (IRF) family of transcription factors, mediate many changes in the transcriptional profiles of cells. These changes in gene expression are responsible for the biologic activities of IFNs, including the IFN-induced antiviral state that is a cornerstone of antiviral innate immunity (2) and the property by which IFNs were discovered (1).

In the first minireview of the series, Sidney Pestka at Robert Wood Johnson Medical School, Piscataway, NJ in his article entitled “The Interferons: 50 Years after Their Discovery There Is Much More to Learn” provides an account of the discovery of interferons, their purification and molecular cloning, and the biologic activities of IFNs (6). The second minireview, by Nicole de Weerd, Shamith Samarajiwa, and Paul Hertzog at Monash University in Australia, entitled “Type I Interferon Receptors: Biochemistry and Biologic Functions,” focuses on recent developments in understanding the biochemical properties and functional activities of the type I IFN receptor chains (7). The expression of IFNAR chain forms, the biochemical roles that IFNAR1 and IFNAR2 protein domains play in the signaling process and their regulation, and the importance of IFNAR2 in differential interactions with the multiple type I IFNs are considered (7). Disease associations of polymorphisms in IFNAR genes (7) and therapeutic uses of IFN-α and IFN-β (6) are discussed.

The combined biochemical and genetic studies of the mechanisms by which interferons induce the transcriptional activation of new cellular gene expression led to the discovery of the JAK-STAT signaling pathway. Christian Schindler at Columbia University in New York, David Levy at New York University School of Medicine, and Thomas Decker at the University of Vienna prepared a minireview entitled “JAK-STAT Signaling: from Interferons to Cytokines.” In that minireview they provide an overview of four members of the JAK family of kinases and seven members of the STAT family of transcription factors and then focus on biochemical and structural studies that provide new insights into the mechanisms by which the STAT factors regulate transcription (8). While Stat1 and Stat2 were discovered in studies of type I IFN signaling as components of the ISGF-3 complex, the seven members of the STAT family of transcription factors are now known to transduce signals for a large number of cytokines and growth factors. The regulation of STAT activity, including regulation by posttranslational modifications, and the mechanisms of STAT-dependent transcriptional activation are summarized (8).

The final minireview of this thematic series on interferon signaling and innate immunity focuses on the interferon regulatory factor family of transcription factors and their diverse roles in establishing host resistance against pathogens. Keiko
Ozato, Prafullakumar Tailor, and Toru Kubota at the National Institutes of Health in Bethesda in their minireview entitled “The Interferon Regulatory Factor Family in Host Defense: Mechanism of Action” describe the mechanisms by which IRFs play critical roles in both innate and adaptive immunity, including the induction and action of the IFNs (9). The biochemical properties of the IRF proteins and the molecular mechanisms by which the nine IRF family members regulate gene expression by both IFN-dependent and -independent mechanisms are described.

The elucidation of the signal transduction pathways responsible for the induction and action of interferons has contributed fundamental new insights relevant to many areas of molecular cell biology and biochemistry. The authors and editors hope that this thematic series of minireviews that focuses on the interferon system will enable investigators in the basic and clinical sciences to better appreciate the properties of interferons and their receptors, as well as the mechanisms by which IRF and STAT transcription factors function to mediate changes in gene expression that are responsible for many of the pleiotropic activities attributed to IFNs, including their antiviral activity.

REFERENCES
1. Isaacs, A., and Lindenmann, J. (1957) Proc. R. Soc. London Ser. B Biol. Sci. 147, 258–267
2. Samuel, C. E. (2001) Clin. Microbiol. Rev. 14, 778–809
3. Yoneyama, M., and Fujita, T. (2007) J. Biol. Chem. 282, 15315–15318
4. Uematsu, S., and Akira, S. (2007) J. Biol. Chem. 282, 15319–15323
5. Hiscott, J. (2007) J. Biol. Chem. 282, 15325–15329
6. Pestka, S. (May 14, 2007) J. Biol. Chem. 282, 10.1074/jbc.R700004200
7. de Weerd, N. A., Samarajiwa, S. A., and Hertzog, P. (May 14, 2007) J. Biol. Chem. 282, 10.1074/jbc.R700006200
8. Schindler, C., Levy, D. E., and Decker, T. (May 14, 2007) J. Biol. Chem. 282, 10.1074/jbc.R70000200
9. Ozato, K., Tailor, P., and Kubota, T. (May 14, 2007) J. Biol. Chem. 282, 10.1074/jbc.R700003200