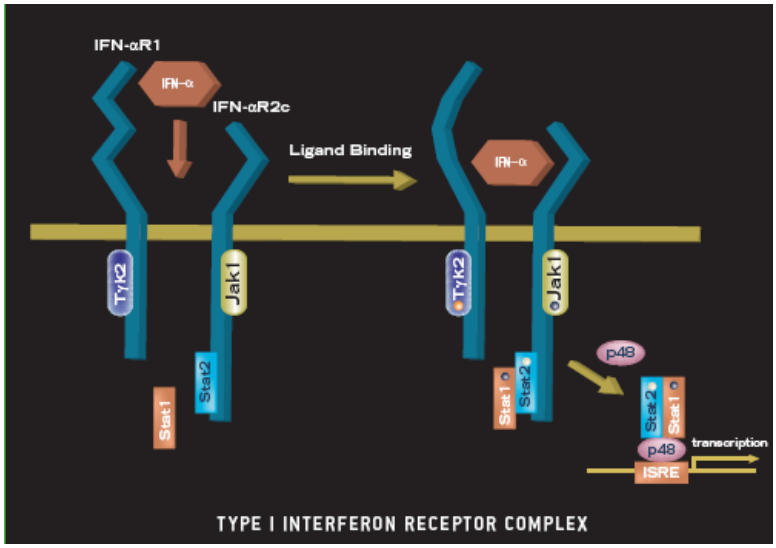
Introduction to Interferon

Interferons (IFNs) are a family of mammalian cytokines initially characterized by their ability to inhibit viral infection. In addition to their antiviral properties, IFNs have also been shown to exhibit antiproliferative, immunomodulatory, and many other activities.

IFNs are classified as Type I or II based on receptor complex recognition and protein structure. Mammalian type I IFNs consist of over nine distinct classes that include IFN-α, IFN-β, IFN-δ, IFN-ε, IFN-κ, IFN-ω, IFN-υ, IFN-τ and IFN-ζ. While IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, and IFN-υ are found in humans, IFN-δ, IFN-τ and IFN-ζ are not. These IFNs bind to the type I receptor which is composed of two chains, commonly designated IFNAR1 and IFNAR2. Type I IFNs are typically produced by macrophages, neutrophils, dendritic cells and other somatic cells in response to many viruses and some pathogens.



In humans, IFN-α consists of a group of proteins that are greater than 85% homologous by amino acid sequence. Only one human IFN-α is N-glycosylated and a few IFN-α species have been shown to be O-glycosylated. In the mouse, nearly all of the IFN-α species are N-glycosylated. IFN-β, is produced by a variety of cells in response to viral challenge, and the native human IFN-β bears a single N-glycosylation site. The other type I IFNs have not been studied extensively as IFN-α and IFN-β. Type II IFN in humans is limited to a single IFN-γ gene. This IFN binds to the Type II receptor comprised of IFNGR1 (IFN-γR1) and IFNGR2 (IFN-γR2) chains. IFN-γ is produced by cells of the immune system such as T-cells and NK cells. IFN-γ is glycosylated in mammalian cells, and functions as a homodimer. On a mass basis, IFN-α and IFN-β exhibit more potent antiviral activity than IFN-γ.

Often, the expression of the type I IFNs is induced by engagement of Toll-Like Receptors (TLR). The innate immune system has evolved the ability to recognize non-self motifs through the TLR receptors, *e.g.,* double stranded RNAs through TLR3, lipopolysaccharides through TLR4, and methylated CpG DNA motifs through TLR9. Interferon produced by TLR-activated cells can function in an autocrine or paracrine manner limiting pathogen infection. When IFN interacts with its cognate receptor, a signal is rapidly transmitted within the cell, often producing an antiviral state. The primary signal transduction cascade promoted by type I IFNs is the JAK1-STAT pathway (see below).

Activation of this signal transduction pathway leads to increased gene expression including (2'-5') oligoadenylate synthetases, Mx proteins, and protein kinase R (PKR) that protect the cell from viral infection. In fact, a host of genes are expressed in response to interferons many of which have roles yet to be determined.

It remains unclear why there are so many different Type I IFNs including multiple IFN-α subtypes. A variety of studies suggested they possess overlapping but also unique sets of biological activities. Additional studies are revealing that type I IFNs may also play immunoregulatory roles. In contrast, the primary role of IFN-γ is the activation and development of adaptive immune functions with a lesser role in innate immune responses. Despite fifty years of intense research, there are still many unanswered questions regarding interferons.