DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Interferons (IFNs) are a group of signaling proteins made and released by host cells in response to the presence of several pathogens, such as viruses, bacteria, parasites, and also tumor cells. Interferons stimulate the infected cells and those nearby to produce proteins that prevent the virus from replicating within them. Further production of the virus is thereby inhibited and the infection is stemmed. Interferons also have immunoregulatory functions—they inhibit B-lymphocyte (B-cell) activation, enhance T-lymphocyte (T-cell) activity, and increase the cellular-destruction capability of natural killer cells.

Interferons (IFN) represent a family of cytokines which can be divided into three groups: type I (IFN-I), IFN-II and IFN-III. IFN-I present in humans are IFN-α, IFN-β, IFN-ε, IFN-κ and IFN-ω. In general, IFN-I are produced when the body recognizes a virus has invaded it. They are produced by fibroblasts and monocytes. Once released, IFN-I will activate molecules which prevent the virus from producing and replicating its RNA and DNA. IFN-II interferon is secreted only by natural killer cells and T lymphocytes; its main purpose is to signal the immune system to respond to infectious agents or cancerous growth. Although discovered more recently than IFN-I and IFN-II, recent information demonstrates the importance of IFN-III in some types of virus infections.

By interacting with their specific receptors, IFNs activate signal transducer and activator of transcription (STAT) complexes; STATs are a family of transcription factors that regulate the expression of certain immune system genes. STAT activation initiates the most well-defined cell signaling pathway for all IFNs, the classical Janus kinase-STAT (JAK-STAT) signaling pathway. Thus, IFN-I and IFN-II induce IFN-stimulated gene (ISG) expression by phosphorylating STAT1 and/or STAT2, mediated by Janus kinases (Jaks). STAT1 homodimers (in response to IFN-I and IFN-II) or STAT1-STAT2 heterodimers (in response to IFN-I) directly activate genes containing the IFN-II activated site (GAS) DNA element. Association of STAT1-STAT2 heterodimers or STAT2 homodimers with interferon regulatory factor (IRF) 9, in response to IFN-I, expands the range of enhancer elements that can be targeted by the JAK-STAT pathway to interferon stimulated response element (ISRE). Similarly, IRF1 can regulate expression of ISGs in response to IFN-I and IFN-II by directly binding the ISRE or IRF-responsive element (IRE). The similarities and differences in the biological properties of IFN-I and IFN-II may be a reflection of the partially overlapping and differential activation of transcription factor complexes and regulation of cellular genes by the two types of IFNs.

For a deeper understanding of the complexity of this system, in this project we propose to perform experiments using contemporary whole-genome approaches of molecular biology such as Next Generation Sequencing (NGS) as well as Chromatin Immunoprecipitation-sequencing (ChIP-Seq). These techniques allow specifying how specific STAT and IRF complexes interact with chromatin and how they regulate transcriptional activity of particular ISGs, depending on the type of interferon and the time of exposure. Using knock-out and over-expression systems and DNA-binding assays of different STATs and IRFs and ISRE and GAS mutation techniques, we plan to resolve the mechanism of transcriptional regulation of a novel group of ISRE and GAS composite containing genes in response to IFN-I and IFN-II in different cell types. We also plan to prove that a similar mechanism is responsible for the positive feedback regulation of the STAT1, STAT2, IRF9 and IRF1 genes, and that this is instrumental in driving long-term IFN responses. Furthermore, by performing anti-viral, anti-proliferative and pro-apoptotic assays we will be able to further assess a role of this novel IFN signaling pathway and some of these novel genes in IFN biology. These studies will shed light on so far unclear issues concerning the complexity of the innate immune response, which in the future could give the foundation for origin of new, more effective antiviral drugs, and may also result in the discovery of biomarkers for monitoring the course of viral infection and its treatment.