MIT Chemical Engineering Department & Ragon Institute
Spring 2021 Seminar Series
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Dynamic Control of Interferon Signaling and Gene Regulation and Its Role in Regulating the Immune Response

Catera Wilder

Postdoctoral Fellow
UCLA Microbial Pathogenesis Trainee
Signaling Systems Laboratory
University of California, Los Angeles

Wednesday, March 10, 2021
12:00-1:00PM

Abstract: Interferons (IFNs) are cytokines that coordinate the innate immune response to prevent the spread of viral infections. The importance of the IFN response has been recently highlighted, as misregulated IFN expression has been correlated with COVID19 disease severity. Two IFN families (i.e. type I and III IFNs) are responsible for suppressing viral replication, but only type I IFNs induce an inflammatory response, which can be tissue destructive if not properly regulated. As both type I and III IFNs activate the same transcription factor, IFN-stimulated gene factor (ISGF3), it remains unclear how they elicit differential gene expression programs. We found that in lung epithelial cells IFN-β and IFN-λ3 induced multi-phasic ISGF3 responses that differ in prominent dynamic features. In order to determine the underlying mechanisms of this IFN-type-specific response, we pursued a mechanistic systems biology approach – involving iterative mathematical modeling and quantitative experimentation – that revealed several nested positive and negative feedback and feedforward loops whose precise timing and strength determine ISGF3 dynamics. Gene expression analysis revealed IFN-type specific gene induction. These results suggest that IFN-induced gene expression programs in lung epithelial cells may be regulated by the dynamics of ISGF3 activity, which are IFN type-specific and determined by coordinated feedback and feedforward loops. Understanding the control of the JAK-STAT signaling pathway between type I and type III IFNs and identifying key IFN type-specific control mechanisms may enable novel therapeutic strategies to address type I IFN misregulation in a variety of inflammatory and autoimmune diseases.