Deciphering the modulation of gene expression by type I and II interferons combining 4sU-tagging, translational arrest and in silico promoter analysis.

Interferons (IFN) play a pivotal role in innate immunity, orchestrating a cell-intrinsic anti-pathogenic state and stimulating adaptive immune responses. The complex interplay between the primary response to IFNs and its modulation by positive and negative feedback loops is incompletely understood. Here, we implement the combination of high-resolution gene-expression profiling of nascent RNA with translational inhibition of secondary feedback by cycloheximide. Unexpectedly, this approach revealed a prominent role of negative feedback mechanisms during the immediate (<=60 min) IFN? response. In contrast, a more complex picture involving both negative and positive feedback loops was observed on IFN? treatment. IFN?-induced repression of genes associated with regulation of gene expression, cellular development, apoptosis and cell growth resulted from cycloheximide-resistant primary IFN? signalling. In silico promoter analysis revealed significant overrepresentation of SP1/SP3-binding sites and/or GC-rich stretches. Although signal transducer and activator of transcription 1 (STAT1)-binding sites were not overrepresented, repression was lost in absence of STAT1. Interestingly, basal expression of the majority of
these IFN?-repressed genes was dependent on STAT1 in IFN-naïve fibroblasts. Finally, IFN?-mediated repression was also found to be evident in primary murine macrophages. IFN-repressed genes include negative regulators of innate and stress response, and their decrease may thus aid the establishment of a signalling perceptive milieu.

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