

# Interactions between microRNAs and Interferon Signal Pathway: An Ongoing Battle between Virus Infection and Host Immune Response

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Over the last decade, RNA molecules with ~20–30 nucleotide in length have emerged as critical regulators in the expression and function of eukaryotic genomes. Small (~20–30 nucleotide [nt]) noncoding RNAs (microRNA, miRNA) can regulate genes and genomes and this regulation can occur at some of the most important levels of genome function, including chromatin structure, chromosome segregation, transcription, RNA processing, RNA stability and translation. The function of miRNA regulation of gene expression is highly dependent on the context and location of miRNA seed sequence, and the degree of complementary between the miRNA seed sequence and mRNA target sequence [1]. The first microRNA, lin-4 from *Caenorhabditis elegans*, was discovered by Ambros and coworkers in 1993 as an endogenous regulator of genes that control developmental timing. In 2001, miRNAs were found to comprise a broad class of small RNA regulators, with at least dozens of representatives in each of several plant and animal species [2]. MiRNAs can regulate endogenous gene expression as described in many literatures [3,4]. Among all those are genes that encode interferons (IFNs). IFNs are cytokines that are spontaneously produced in response to virus or other pathogen infection. They function through binding to different IFN-receptors (IFN-R), which triggers down-stream cell signalling and the subsequent induction of hundreds of IFN-stimulated (sensitive) genes (ISGs), including both protein-coding and non-coding microRNA genes. IFNs can block viral replication and stimulate the host immune response through this process. Conversely, by regulating the expression of interferon genes, some miRNAs have the ability of inhibit or stimulate viral replication in cells directly or indirectly. The regulative function of microRNAs can be exerted all through the IFN signal pathway. In contrast, IFNs can affect the expression of miRNA in host cells. For example, to test whether IFN could alter the expression of cellular miRNAs, Pedersen et al. used microarray technology to analyse RNA derived from IFN $\alpha$ / $\beta$ - or IFN $\gamma$ -stimulated cells. This initial screening effort identified ~30 miRNAs, the expression levels of which were increased or attenuated in response to IFN $\alpha$ / $\beta$  or IFN $\gamma$  [5]. The mechanism of the phenomenon may be that IFNs are potentially important regulators of Dicer expression, which is a key enzyme in the generation of miRNAs [6].

## IFN Induces miRNA Expression

IFNs can be categorized into three classes (type I, II and III), dependent on the receptor molecules that they interact with. Type I IFNs and virus infection can directly induce the expression of miRNAs. Some of these IFN-induced miRNAs have been shown to have direct anti-viral activity. For example, at least eight miRNAs were induced in response to IFN $\beta$ , displaying RNA sequence specificity with the human hepatitis C virus genome, and of these, miRNA-351, miRNA-431 and miRNA-488 can functionally inhibit HCV replication [5]. Similarly miRNA-29a, which is also IFN $\alpha$ / $\beta$  inducible, has sequence homology to the 3'UTR of HIV genome and can inhibit the replication of HIV [7]. Thus IFN-inducible miRNAs serve as clear examples that some miRNAs have direct anti-viral activity and therefore comprise a critical component of the IFN anti-viral mechanisms. It was estimated that type II IFN(IFN $\gamma$ ) directly induces over 100 miRNAs in human cells,

many of the cellular targets of these miRNAs are not confirmed and/or unknown. However, what is known is that miRNA-29 is up-regulated by IFN $\gamma$  signalling through STAT-1, although this has not been demonstrated in the context of virus infection [8].

## miRNAs Modulate IFN Signaling Pathway

Conversely, some miRNAs can regulate expression of genes involved in IFN signaling pathway. These miRNAs share sequence homology with IFNs, IFN-Rs, or IFN signalling molecule mRNA sequences and thus can down-regulate their expression. There are a large number of miRNAs that subvert almost all aspects of the IFN cascade. For example, miR-22, a miRNA directly targeting high mobility group box-1 (HMGB1) and interferon regulatory factor 5 (IRF-5), prevents activation of IRF-3 and NF-kappa B, and thus ultimately inhibits IFN production [9]; Higher level of miRNA-155 has been shown to decrease the level of suppressor of cytokine signaling 1(SOCS1) protein which is induced early in the IFN response and play an important role in IFN desensitization [10]. miRNA-211, 222, 145 can down-regulate the expression of signal transducers and activators of transcription 1 (STAT-1) protein which plays important role in the signaling through any of the IFN receptor complexes [11,12]. miRNA-182, 183, 200a/b can impede the translation of interferon-stimulated gene 15 (ISG15) protein which have multiple functions in various viral infections [1]. miRNA-155 can target the 3'-UTR of the IFN $\gamma$ R $\alpha$  mRNA and it is demonstrated that reduced miRNA-155 results in increased IFN $\gamma$ R expression and IFN-responsiveness [13]. Type III IFNs comprise IFN $\lambda$ 1 (IL-29), IFN $\lambda$ 2 (IL-28A) an IFN  $\lambda$ 3(IL-28B) and are most recently discovered cytokines, with similar activities to Type I IFNs, but type III IFNs bind to a distinct IFN receptor, the IFN $\lambda$ R1 (otherwise known as the IL-28R-IFN $\lambda$ ) which complexes with IL-10R2. Type III IFN genes are also regulated by miRNAs. Bioinformatics analysis predicts multiple 3'-UTR sites for miRNA binding within the IFN $\lambda$ 1 gene sequence, and miR-548 has been experimentally shown to down-regulate the expression of IFN $\lambda$ 1 [14].

## Conclusion

Type I IFNs (IFN $\alpha$ / $\beta$ ) are the major components in innate immunity to combat viral infection and work synergistically with numerous IFN-regulated genes or IFN-stimulated genes which include both protein-

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coding and non-coding genes. miRNAs obviously play an important role in regulating the cellular responses to IFNs and to virus infection. Although some IFN-induced miRNAs have direct anti-viral activity, some virus-encoded miRNAs interfere with IFN and/or ISGs to create an pro-viral environment to facilitate viral replication. The outcome of virus infection is therefore dependent on a fine balance of pro- and anti-viral factors, comprising IFNs, ISGs, and cellular and viral miRNAs.

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