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Review

microRNA control of interferons and interferon induced anti-viral activity

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ABSTRACT

Interferons (IFNs) are cytokines that are spontaneously produced in response to virus infection. They act by binding to IFN-receptors (IFN-R), which trigger JAK/STAT cell signalling and the subsequent induction of hundreds of IFN-inducible genes, including both protein-coding and microRNA genes. IFN-induced genes then act synergistically to prevent virus replication and create an anti-viral state. miRNA are therefore integral to the innate response to virus infection and are important components of IFN-mediated biology. On the other hand viruses also encode miRNAs that in some cases interfere directly with the IFN response to infection. This review summarizes the important roles of miRNAs in virus infection acting both as IFN-stimulated anti-viral molecules and as critical regulators of IFNs and IFN-stimulated genes. It also highlights how recent knowledge in RNA editing influence miRNA control of virus infection.

1. Introduction

Interferons (IFN) comprise a diverse group of structurally unrelated molecules that are naturally produced in response to virus infection. These cytokines were called "interferons" simply because they "interfere" with virus replication. IFNs do this by acting in an autocrine manner, directly influencing the virus-infected cells in which they are produced. However, because they are secreted molecules, they can also simultaneously affect neighbouring uninfected cells to create an "anti-viral state" in surrounding uninfected cells. IFNs induce the expression of genes that are transcriptionally activated as a result of IFN-receptor (IFN-R) signalling. In mammalian cells there are hundreds of genes that are IFN-inducible (IFN-stimulated genes; ISG), and many, although not all of these molecules have functions that inhibit virus replication in some way or other (Sadler and Williams, 2008). While IFN research has historically focused on interferons themselves or on interferon-induced proteins, IFNs also influence the expression of a number of non-coding RNA genes, especially micro RNA (miRNA). Therefore IFNs, ISG, and miRNA, act synergistically to create a potent virus non-specific cellular environment that is non-permissive for virus replication (Sedger et al., 1999) (REFS) and together these protein and RNA molecules comprise a cells innate response to virus infection.

2. microRNA (miR): biogenesis and functions

microRNAs (miRNA or miR) are small non-coding RNAs that are generally 22 nucleotides in length. Although first described in nematodes (Lau et al., 2001; Lee and Ambros, 2001), they are highly homologous across diverse animal and plant phyla (Lagos-Quintana et al., 2001) and encoded within diverse viral genomes (Ding and Lu, 2011). Mammalian miRNA genes often exist as non-coding genes located within intergenic regions of genomes, but they also exist within both exonic and intronic regions of protein-coding genes (Kapinas and Delany, 2011), and alternate exon splicing can regulate the expression of intronic miRNA genes (Melamed et al., 2013). Most miRNA genes are transcriptionally controlled by RNA polymerase II, transcription factors (Brueckner et al., 2007; O'Donnell et al., 2005) and DNA methylation (Szenthe et al., 2013) (for review on miRNA gene regulation see (Breving and Esquela-Kerscher, 2010). Many miRNA are also post-transcriptionally regulated (Wulczyn et al., 2007) and infact miRNA biogenesis occurs in several steps, all of which are tightly controlled (Tran and Hutvagner, 2013). miRNA genes are present singly or in clusters and are initially expressed as a long pri-miRNA precursor molecules which range from hundreds to thousands of nucleotides in length (Rodriguez et al., 2004; Saini et al., 2007). Most pri-miRNAs are then trimmed by Drosha (aided by the dsRNA binding protein DGCR8 (DiGeorge syndrome critical region gene 8 and the nuclear microprocessor complex), into pre-miRNAs, that

Abbreviations: ADAR, adenosine deaminase acting on RNA; APOBEC, apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like; IFN, interferon; IFN-R, interferon receptor; IRF, interferon regulatory factor; JAK, janus kinase; miR or miRNA, microRNA; NO, nitric oxide; OAS, oligo adenylate synthase; PKR, protein kinase R; RISC, RNA induced silencing complex; STAT, signal transducers and activators of transcription.

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are shorter hairpin structures of about 70 nucleotides in length (Denli et al., 2005; Lee et al., 2003). Given that miRNA genes are generally located within introns, they can sometimes also give rise to pre-miRNAs via intron splicing events, i.e., independently of Drosha (Ruby et al., 2007). Pre-miRNA molecules are then exported out of the nucleus via association with nuclear export molecules such as exportin-5 and RAN-GTP (Yi et al., 2003). Outside the nucleus the pre-miRNA then associates with Dicer and TAR RNA-binding protein, to yield a short double-stranded 22nt miRNA duplex: miRNA-miRNA* (Lee et al., 2002; Zhang et al., 2002). Here, one strand of the miRNA complex is then loaded onto the Agonaute-2 protein and forms the minimal RNA Induced Silencing Complex (RISC) (Hutvágner and Zamore, 2002). Using the miRNA as a "guide", a RISC mediates binding of the miRNA to complementary sequences located within target mRNAs (Hutvagner, 2005) which usually results in target gene silencing by mRNA degradation or translational inhibition (Fig. 1). In general the miRNA:mRNA homology dictates the target mRNA molecules' fate (Zeng et al., 2003); complete nucleotide complementarity within the 7–8 nucleotide "seed sequence" usually results in mRNA cleavage (Valencia-Sanchez et al., 2006), whereas miRNA molecules with partial or incomplete complementarity frequently cause translational inhibition of the mRNA (Beilharz et al., 2009; Humphreys et al., 2005) (Fig. 1). Alternatively miRNAs can occasionally enhance RNA stability, and even enhance viral RNA replication. It is thought that they do this by shielding the mRNA template from RNAse degradation (Li et al., 2013a).

It is believed that there are over 700 human genome encoded miRNA genes (there are over 1000 miRNA molecules and greater than 24,000 miRNA entries in the miRBase Registry (version 20: http://www.mirbase.org/) (Griffiths-Jones et al., 2008). In contrast, bioinformatics searches for miRNA seed sequence complementarity motifs within mRNAs indicate that there are thousands of genes with potential "target" sequences. Therefore miRNA can have multiple complementary target mRNAs and they are believed to control expression of up to two-thirds of all mammalian genes (Lewis et al., 2005; Xie et al., 2007). In this regard it is evident that the target sequences may lie within different regions of mammalian genes and as such miRNA can influence mRNA expression in a variety of ways (Fig. 1). Most commonly miRNA seed sequence

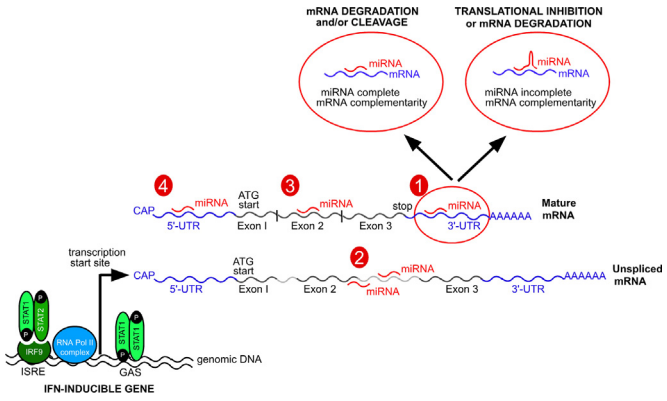

Fig. 1. miRNA seed sequence complementarity gene location effects. IFN-inducible gene expression results in mRNAs with classical features including 5′-untranslated regions (UTR) with CAP structures, introns and 3′-UTR with poly(A) termini. These mRNAs are then spliced and processed into mature mRNAs with contiguous protein-coding open reading frames (ORFs). However, miRNA may have seed sequence complementarity to any region of the unprocessed or mature mRNA. miRNAs can target the 3′-UTR (1), but they may also show complementarity to intronic regions including intron/exon junctions (2), exonic coding regions (3) or 5′-UTRs (4). The function of the miRNA is then largely dependent on the degree of complementarity with the target mRNA, with a complete match usually resulting in mRNA cleavage or degradations, and incomplete matches likely mediating mRNA translational inhibition.

complementarity lies within the 3′-untranslated regions (UTR) of genes (Lai, 2002; Lewis et al., 2005) and miRNA binding at this location usually results in RNA degradation or translational inhibition (depending on the extent of homology between the miRNA see region and mRNA target, as discussed above). miRNA seed region homology can also exist within introns of protein-coding genes (Ying and Lin, 2005), or reside within 5′-UTR regions of genes, and hence they can negatively directly influence transcriptional regulation of target genes, not just mRNA stability or expression (Abdelmohsen et al., 2008). Conversely, there are also now examples of 5′-UTR-binding miRNA that can enhance mRNA expression (Janowski et al., 2007; Li et al., 2007a) potentially acting to improve mRNA stability. In summary miRNA regulation of protein gene expression is highly influenced by the context and location of the miRNA seed sequence, and degree of complementary between the miRNA seed sequence and mRNA target sequence. With respect to virus infection, miRNA not only target cellular genes that function to permit or inhibit virus replication, but they can exhibit a direct anti-viral activity in their own right by targeting viral mRNAs (Lecellier et al., 2005) (see Table 1). Similar to cellular mRNAs, miRNA targeting viral open reading frames (ORFs) cause degradation of viral mRNAs to regulate virus replication. Thus miRNA are critical players in the regulation of viral and cellular gene expression and they constitute an independent layer of regulation of gene expression. This review will now summarize what is known about miRNAs as regulators of IFNs and IFN-inducible anti-viral effector molecules.

3. Interferons (Ifns) and miRNA

3.1. Type I IFNs and IFN-inducible miRNA

IFNs were first defined as molecules released from virus-infected cells that act to inhibit virus replication (Isaacs and Lindenmann, 1957). They are produced by cells in response to viral nucleic acid, notably, but not exclusively, dsRNA, which is an intermediate nucleic acid produced during virus replication and therefore present within most virus infected cells. Interferons are also produced in response to artificial nucleic acids such as polyinosine-polycytidylic acid (polyI:C), a synthetic analogue of dsRNA (Hilleman, 1970; Richmond and Hamilton, 1969). The production of IFNs is largely transcriptional; they are not pre-formed and stored within cells. Their expression is rapid and dramatic, that is, they are quickly produced early after infection and often in large amounts. For many type I IFNs the process begins through viral nucleic acid acting as a ligand for intracellular Toll-like receptor (TLR) molecules, whereby dsDNA binds TLR-3, and ssRNA binds TLR-7. Since these TLRs are frequently present within endosomes they are present within the same sub-cellular compartment as viruses that enter cells via receptor mediated endocytosis (Jensen and Thomsen, 2012). TLRs then induce intracellular signalling involving Myeloid differentiation primary response gene (MyD88) or TIR-domain-containing adapter-inducing IFNβ (TRIF), which results in the activation of IFN regulatory factor (IRF)-3, IRF-7, and Nuclear Factor-kappa beta (NFκB), and the subsequent transcriptional activation of type-I IFN gene promoters, especially IFNα and IFNβ (for review see Sasai and Yamamoto, 2013). However, IFN can be induced by other mechanisms, for example by retinoic-acid-inducible protein I (Rig-I) helicase and melanoma-differentiation-associated gene 5 (MDA5) detection of viral RNA present in the cytoplasm of virus-infected cells (Kato et al., 2006) (for review see Hovanessian, 2007). Either way, type I IFNs are quickly produced in virus-infected cells, by virtue of the cell "sensing" or detecting the presence of viral nucleic acid.

IFN are categorized into three classes, dependent primarily on the receptor molecules that they interact with. Type I IFNs