Review Article

Host-Virus Interaction: Role of miRNA and Bioinformatics Tools for miRNA Target Prediction

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Abstract | MicroRNAs (miRNAs) are the small endogenous regulatory non-coding RNAs of approximately 22 nucleotide lengths and are the players of post-transcriptional gene silencing in eukaryotes. miRNAs are the crucial factor in a diverse biological processes such as antiviral defence, oncogenesis and development in higher eukaryotes. When a virus encounters a host there is a complex network of interaction exist defining both host and virus. Though there is several class of factors or molecules involved in that interaction, the role of miRNAs cannot be ignored here. Host encodes its own miRNAs and virus does it's too. Both the systems work for their own benefits. From this crosstalk we can deduce four relationships between the miRNAs of both host and virus for our better understanding. These are host encoded miRNAs interact with host as well as virus and similar interaction can be for viral miRNAs too. The investigation of this complex relationship deduces some of the important points regarding the molecular pathogenesis of the virus and opens a wide path for the suitable strategy to combat the ill effect of the virus. At present several bioinformatics tools are available for the prediction of miRNAs and its target sequence through suitable algorithms pertaining to their own method. So in a vast of whole genome data, miRNA and its target identification is no longer a tedious job. This review focuses on the complete interactions between host and viruses and several bioinformatics tools available with us for its interpretation.

Keywords | microRNA, Non-regulatory RNAs, Post-transcriptional gene silencing, Antiviral defense, Oncogenesis

INTRODUCTION

MicroRNAs (miRNAs or miRs) are the small, non-coding, regulatory, functional and endogenously produced RNA molecules of approximately 22 nucleotide in length and mediate gene expression post-transcriptionally (Scaria et al., 2007; Bartel, 2004; Sullivan et al., 2005; Kumar et al., 2013; Srinivasan et al., 2013). Initially discovered in *C. elegans* and now widely distributed through several strata of taxonomy (Ghosh et al., 2009). The miRBase is an online database that contains published microRNA sequences data and its annotation. The latest release of miRBase is Release 21 which contains 28645 hairpin structured precursor miRNAs, 35828 nos. mature miRNAs in 223 different species (Griffiths-Jones et al., 2008; Kozomora et al., 2014). miRNAs are the key regulators of several biological processes, gene expression pattern and biomarker for diseases (Pritchard et al., 2012). miRNA mediate the gene expression either by target mRNA decay or translational repression. The former mostly seen in case of perfect complementarity as observed in plants while later mechanism in animals due to imperfect complementarity (Ambros, 2004; Ghosh et al., 2009). miRNAs have several functions including regulation of cell physiology, proliferation, cell differentiation, apoptosis, hematopoiesis, limb morphogenesis, fat metabolism (Srinivasan et al., 2013), oncogenesis and viral infection. Several reports suggested aberrant expression profiles of miRNAs

in various human diseases, thereby visualize the concept of miRNA-based therapeutics (Stenvang et al., 2012; Mendell and Olson, 2012; van Rooji and Olson, 2012; Thorsen et al., 2012; van Rooji and Kauppinen, 2014). Lauring et al. (2010) proposed use of miRNA as one of the methodology for preparing live attenuated virus (LAV) vaccine, thus expanding the horizon of the miRNA work sphere. Controlled gene expression by miRNAs suppress tumor growth by regulating the factors of immune system put forward the concept of miRNA as vaccine candidate in case of cancer little further (de Rosa et al., 2014). Due to involvement in multiple biological processes miRNAs are the potential targets for designing new, modern therapeutic to combat cancer and viral diseases.

MATURATION AND PROCESSING OF miRNAs

The linear canonical pathway (most common) of miRNA biogenesis comprises of two distinct phase i.e. the nuclear phase and the cytoplasmic phase. The generation of the primary miRNA (pri-miRNA) transcript of around 200 nucleotide to several thousand nucleotides length by RNA polymerase II enzyme (mostly) or by RNA polymerase III (rarely) (Winter et al., 2009) is the starting point in miRNA biogenesis (Gottwein et al., 2008; Ghosh et al., 2009; Skalsky et al., 2010). The nuclear RNase III enzyme Drosha along with accessory protein DGCR 8 further trim the pri-miRNA to generate precursor miRNA (Pre-miRNA) of 60 nucleotide length (Zhuo et al., 2013). The nuclear phase accomplished with the transportation of pre-miRNA into cytoplasm by the factor exportin-5 conjugated with RanGTP (Kim, 2004). GTP hydrolysis leads to the release of pre-miRNA into cytolplasm. At the onset of cytoplasmic phase the pre-miRNA is cleaved by Dicer (a cytoplasmic RNase III like enzyme) in association with its cofactor TRBP (Transactivating region RNA-binding protein (Winter et al., 2009). This in turn forms miRNA duplex intermediate (miRNA*/miRNA). Dicer loads one of the miRNA strand i.e. the guide strand (miRNA*) into RISCs (RNA induced silencing complexes), which is the miRNA effector complexes (Gottwein et al., 2008; Ha et al., 2014). The non-associated strand i.e. the passanger strand is subsequently degraded. RISC basically comprises of guide miRNA strand and one of the four Argonaute proteins. The miRNA in RISC then targets the complementary mRNA, which is either cleaved in case of perfect complementarity or undergone translational repression in case of imperfect complementarity. miRNA interaction can also leads to deadenylation or target decapping and results in rapid mRNA decay (Wu et al., 2006; Kumar et al., 2013). Translocation of the miRNA:mRNA complex to cytoplasmic foci is another method of translational repression (Kumar et al., 2013).

miRNA AND COMPETITIVE VIRAL AND HOST RNAS (CVHRNAS)

When a virus attacks a host cell, the viral transcript can act as a template for expressing its own proteins or can be a pathogen-associated molecular pattern (Goubau et al., 2013). In a virus infected cells there exist a complex network of interaction between the virus and host cell itself. The pool of common miRNAs means those miRNAs which can bind to both virus and host transcripts as well due to sequence complementarity, present at that moment affect the gene expression pattern of both virus and host. By observing these facts (Li et al., 2014) proposed the "competitive viral and host RNAs (cvhRNAs) hypothesis". As per this hypothesis the viral miRNA able to snatch away the target sequence of host encoded miRNAs thus interfering the stability and translational efficiency of host mRNAs. Same is the case applicable for host miRNA to encounter viral pathogenesis. Thus the competitive environment interaction is the deciding factor for the viral infection to cherish or perish.

HOST-VIRUS INTERACTION FROM miRNA WINDOW

There are several reports indicating the miRNA from virus which targets both viral mRNA and cellular mRNA to favour its existence in host environment. Similarly host produces its own miRNA that interacts with viral mRNA to favour itself, but reports also suggest the synergistic action of host miRNA with viral mRNA. So basically the interaction can be studied as follows.

DUAL ACTIONS OF VIRAL miRNA
Viral miRNA can target both viral and host transcripts and favor its existence in the host. The clear motive of this interaction duo is successful establishment of the viral infection in the host. This can be fulfilled by actions like (i) latent and lytic life cycle balance for persistence of virus, (ii) immune evasion, (iii) prevention of apoptosis, (iv) viral replication regulation, (v) host cell cycle regulation and (vi) other measures (Takane et al., 2011). It is not possible to enlist all suitable examples under each category. Some of the examples are discussed below.

A. VIRAL miRNA AIM FOR VIRAL TRANSCRIPTS
Determination of the targets for viral miRNA on viral transcript is straight and quite easier due to simplicity of the viral genome. Viral miRNAs that are antisense to viral transcripts can regulate the viral infection in host by any of the above described five mechanisms, thus are potential targets for alleviating the virus infection in host.

For persistence infection virus must go for latent life cycle than lytic phase. Most of the herpes virus exhibit latent type

of infection and miRNAs of virus also support this. For example miR-K12-9 of Kaposi's sarcoma–associated herpesvirus (KSHV) suppresses expression of viral replication and transcription activator (RTA) factor thus maintain the latency (Bellare et al., 2009). Similarly miR-15 of Infectious Laryngotracheitis Virus (ILTV) targets transcriptional activator ICP4 mRNA of ILTV gene and maintain the balance between latent and lytic phase of virus (Waidner et al., 2011). A suitable example of immune evasion action by viral miRNA is seen in SV-40 (Simian virus). Its miRNA i.e. miR-S1 expressed late in the infection but target viral T-antigen, thereby reducing its expression and ultimately results in insensitivity of infected cells to host cytotoxic T cells (Sullivan et al., 2005). The Epstein Barr Virus (EBV) miR-BART represses viral LMP-1 protein that promotes host cell apoptosis. Thus prevent cell death and enhance virus survival (Lo et al., 2007). Role of viral miRNA regulating the viral replication through targeting immediate early viral protein can be visualized from Herpes Simplex Virus (HSV) infection (Tang et al., 2008; Umbach et al., 2009). miR-H2 of HSV-1 and HSV-2 targets ICP0 and down regulation of ICP0 protein expression (Umbach et al., 2010) leads to a strong latent stage of infection.HSV-1 miR-H6, which expressed during latency, suppress ICP4 and control viral replication and maintain latency (Munson and Burch, 2012; Mollaie et al., 2013). ICP34.5 is situated antisense to miR-H3 and miR-H4. ICP34.5 is a virulence factor which inhibits PKR (Protein Kinase R) activity and attributes to neurovirulence. Represion of ICP34.5 by viral miRNAs may protect infected neurons being destroyed (Tang et al., 2008; Cullen, 2009). Two miRNAs of ILTV lie anti-sense to ILTV ICP4 and down regulate ICP4 expression (Waidner et al., 2011) resulting in latency.

B. Viral miRNA Aim For Viral Transcripts

A virus wants the cell it infected, to be alive for persistence infection. Thus keeping that as a goal, viral miRNAs target those cellular genes that involved in cell proliferation, survival, stress responses and antiviral defence pathways. In order to establish a successful latent infection, viral miRNA can promote viral replication either by prolonging cell survival or escaping the immune system surveillance. For example we can consider the KSHV miRNAs that target thrombospondin 1 (THBS1), a cellular component, whose main function is to inhibit the angiogenesis and cell growth by TGFβ, results in virus infected cells to perish in the system. Thus inhibition of THBS1 by viral miRNAs prevent cell death (Samols et al., 2005). Mostly the viral miRNAs target regulators of cell survival and growth, apoptotic factors so that the virus can maintain the latency. These facts are well supported by the work conducted by Ziegelbauer et al. (2009) on KSHV miR-K5, Choy et al. (2008) on miR-BART5 and Hansen et al. (2010) on KSHV miR-K11 and miR-K 6. Gottwein et al. (2007) reported the role of KSHV miR-K11 in regulating oxida-

tive stress. KSHV miR-K12-3 targets host NFIB and help in latency of infection. Similarly HCMV (Human Cytomegalovirus) miR-UL 112-1, EBV miR-BART2, KSHV miR-K12-7 target host stress induced ligand MICB, thus bypassing the NK cell mediated killing of infected cells (Nachmani et al., 2009; Stern-Ginossar et al., 2007). EBV miR-BART5 targets PUMA, a p53 regulated proapoptotic Bcl2 family member, thereby prevent the apoptosis of virus infected cells (Choy et al., 2008). EBV miR-BHRF1 down regulate CXCL 11, thus surpassing T cell mediated immunity (Xia et al., 2008).

Dual action of cellular miRNAs

Assigning a separate work boundary for host encoded miRNAs and viral miRNA is difficult. In the competitive environment both have to work for their benefits. The function of cellular miRNA is not straight forward as it has both positive and negative impact on viral infection. Antiviral defense, suppression of viral replication is the fruitful outcome of cellular miRNA while supporting viral replication, inhibiting the host innate immunity is the dreaded outcome.

As host encoded miRNAs have dual properties of being positive and negative action, it will be helpful to discuss under these heading rather based on its target. MicroRNA mediated antiviral defence can be seen in mammalian viruses such as primate foamy virus (PFV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Each case by itself enlights interesting aspect of microRNA-mediated host–virus interaction. Cellular microRNA mediating antiviral defence was seen in PFV (Lecellier et al., 2005). PFV replication is efficiently restricted by the cellular microRNA miR-32 targeting viral transcripts. Host miRNA mediated antiviral defense mechanism is seen in case of HCV replication (Pedersen et al., 2007). Cellular miRNAs such as miR-24, miR-93 suppres Vesicular Stomatitis Virus (VSV) replication (Otsuka et al. 2007). These cellular miRNAs target viral large protein and phosphoprotein genes and ultimately block viral replication. Indirect antiviral response by cellular miRNAs can be observed in case of HIV-1 replication (Triboulet et al., 2007; Vlachakis et al., 2013). In the case of hepatitis C, a cell type-specific microRNA (miR-122) targeting the 5′ UTR of the viral transcript and modulate the viral levels. This explains how tissue or cell type-specific microRNAs can influence tropism of viruses (Henke et al., 2008; Shwetha et al., 2013). The microRNAs targeting the viral transcripts were variable in individuals, suggesting that variation in expression levels may define the prognosis of infection.

Cellular miRNAs are helpful in some aspects for viral infection. For example miR-155 of EBV affected B cell prevents apoptosis and inhibits host innate immunity (Linnstaedt et al., 2010). Cellular miRNA miR-132 regulate transcription factor thus have a control in viral replication

as observed in HIV-1 (Chiang et al., 2013), KSHV, HSV-1 and HCMV-1infections (Lagos et al., 2010). miR-122 stimulate HCV viral RNA stability and translation (Roberts et al., 2011). HIV-1 down regulates the expression of several host encoded miRNAs for its efficient replication and may also up regulates those miRNAs that are helpful for its survival (Ghosh et al., 2009).

BIOINFORMATICS TOOLS TO EXPLORE miRNA IN HOST-VIRUS INTERACTION

Being highly complex nature of the miRNA and target interaction, use of bioinformatics tools for prediction of miRNA target is a modern approach and less cumbersome and straightforward (Ekimler et al., 2014). As compared to target prediction for miRNA in plant, which is quite straight and easier, the task in animal counterpart is more functionally diverse in nature (Bartel, 2009). So certain points are to be taken care of while going for miRNA target prediction. These are as follows:

1. The seed sequence i.e. about 2-7 nucleotides at the 5' end of miRNA sequence follow the Watson-crick base pairing with 3' UTR sequence of targeted transcripts. This is indeed essential to confer regulation of miRNA target (Kim, 2004). Along with this seed pairing, there is pairing at 3' end of miRNA called as 3'-supplementary pairing which helps in improving specificity and affinity (Bartel, 2009; Kumar et al., 2013).

2. When there is weaker 5' complementarity, additional compensatory base pairing is required at 3' end of miRNA for regulation (Brenneck et al., 2005). It does not necessarily mean that extensive pairing to the 3' end of miRNA is only sufficient for regulation on its own without a minimal element of 5' complementarity.

3. Identification of a conserved site for miRNA target increases the reliability of prediction programs (Kumar et al., 2013).

4. Target multiplicity means when one miRNA targets several genes suggesting combinatorial control of a single target by multiple miRNAs. This can be an important feature of miRNA targeting, very similar to the mode of transcription factor control of genes (Doench et al., 2004) and multiple binding sites for a miRNA on the 3' UTR can increase the efficiency of RNA silencing.

5. The strength of association between miRNA and its target depends upon the kinetics and thermodynamics properties of the bonding of both, which can be determined by RNA folding programs (Wuchty et al., 1999).

miRNA TARGET PREDICTION TOOL

There are several bioinformatics tools available for the prediction of miRNA targets across species. It is not possible to enlist all. Few are described below.

PicTar

It is an algorithm for prediction of microRNA targets. This website provides details regarding target prediction for miRNA in vertebrates, seven *Drosophila* species and three nematode species. It also gives idea about the co-expressed human miRNA targets which are not conserved. PicTar is the first algorithm for analyzing miRNAs and its targets in co-expression with respect to specific time and place (Krek et al., 2005). It computes a maximum likelihood score for a given transcript is targeted by several numbers of miRNAs. Based upon the most updated PicTar predictions, doRiNA database provides target predictions for human, mouse and worm (Ekimler et al., 2014).

RNAhybrid

RNA-hybrid predicts multiple potential binding sites on target RNA for miRNAs and finds the energetically most favorable hybridization sites (Rehmsmeier et al., 2004). Intramolecular hybridizations i.e. base pairings between target nucleotides or between miRNA nucleotides itself are not allowed. It allows many long targets to be searched in a short time. RNAhybrid, with its accompanying programs RNAcalibrate and RNAeffective, is available for download and as a Web tool on the Bielefeld Bioinformatics Server.

The microRNA.org Resource (Betel et al., 2008)

MicroRNA.org is an exclusive database of microRNA target predictions. Expression profiles and target predictions are based on miRanda algorithm. Here a user can explore (i) genes that are governed by a particular miRNA, (ii) for a single mRNA target several mi RNAs and (iii) miRNA expression profiles in several tissues.

miRanda-micro RNA Target Detection

This algorithm has been written in C languages. MiRanda was developed at the computational biology centre of Memorial sloan-kettering cancer centre. High complementarity between the miRNA and its target is the principle behind the prediction. The algorithm favours complementarity between 5' end of miRNA and 3' end of the transcripts and stability is evaluated by thermodynamically using the Vienna RNA folding packages (Kumar et al., 2013).

mirDIP

mirDIP is the microRNA Data Integration Portal and as the name suggest it admixtures twelve miRNA prediction datasets obtained from six different miRNA prediction databases. Thus improves the accuracy and confidence of target prediction for miRNAs. One can use mirDIP

in three different way of searching such as source search, characteristic search and tailored situation search (Shridel et al., 2011).

Diana microT (DIANA LAB)

Artifical neural network based prediction system is DIana microT 4.0 program. It looks for target genes for those miRNAs that are either user defined or annotated forms of these miRNAs. It calculates and uses the free energy of binding sites as an input data for prediction (Ekimler et al., 2014).

miRTar

It is an integrated web portal for target identification of miRNAs exclusively for human. MicroRNA Target prediction (miRTar) is a tool that enables biologists to identify the biological functions and the regulatory relationship between miRNAs and their transcripts. It also provides perspective of information on the miRNA targets on alternatively spliced transcripts. It supports four major features, such as:

- Identifying miRNA targets in humans.
- miRNA prediction in all possible combinations.
- View point on the regulation between miRNA and RNA alternate splicing.
- Linking of miRNA to metabolic pathway.

ViTa

It is basically a database for host miRNA targets on virus genomes and viral transcripts (Hsu et al., 2007). The database has a collection of known host miRNAs, viral miRNAs and host miRNA targets on viruses. So it will be helpful in investigating host virus interaction through host miRNA window. It acquires virus miRNA data from other databases like miRBase, ICTV, VirGen, VBRC and predict the targets for cellular miRNAs by using miRanda and TargetScan. This is also give idea about human miRNA expression in virus infected tissues. It also helps users to investigate the microRNA roles in viral existence. ViTa was developed by Bidlab in 2005.

CONCLUSION

In case of post transcriptional gene regulation miRNA is an important key factor. The role of miRNA in host- virus interaction cannot be neglected as this interaction opens several pathways to study molecular basis of pathogenesis of virus infection. The relevant study regarding this interaction enlightens the present understanding on possible interaction between host and virus and enriches our knowledge to develop new age vaccine based on miRNA or to develop novel therapeutic strategy to combat virus infection. The manipulation of miRNA in host virus interaction may possible help us to ameliorate the virus infection effectively in near future.

CONFLICT OF INTEREST

The authors have no conflict of Interest.

AUTHORS' CONTRIBUTIONS

Aditya Prasad Sahoo, Ashok Kumar Tiwari and Ravi Kumar Gandham gave the concept of the manuscript and overviewed bioinformatics portion. Amit Ranjan Sahu and Arpita Padhy drafted and revised the whole manuscript. Sajad Ahmad Wani, Amod Kumar and Govindarajan Bhuvana Priya equally contributed matter to the manuscript. All the authors have read and approved the manuscript.

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