

IMMUNOLOGY, HEALTH AND DISEASE

Understanding the cross-talk between host and virus in poultry from the perspectives of microRNA

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ABSTRACT In poultry, viral infections (e.g., Marek's disease virus, avian leukosis virus, influenza A virus, and so on) can cause devastating mortality and economic losses. Because viruses are solely dependent on host cells to propagate, they alter the host intracellular microenvironment. Thus, understanding the virus-host interaction is important for antiviral immunity and drug development in the poultry industry. MicroRNAs are crucial posttranscriptional regulators of gene expression in a wide spectrum of biological

processes, including viral infection. Recently, microRNAs have been identified as key players in virus-host interactions. In this review, we will discuss the intricacies involved in the virus-host cross-talk mediated by host and viral microRNAs in poultry (i.e., chicken and ducks), as well as recent trends and challenges in this field. These findings may provide some insights into the rapidly developing area of research regarding viral pathogenesis and antiviral immunity in poultry production.

Key words: cross-talk, poultry animal, microRNA, viral infection, virus-host

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INTRODUCTION

Many types of viruses will cause high mortality rates and enormous economic losses to the poultry industry. For example, Marek's disease virus (MDV) and avian leukosis virus can induce neoplastic diseases in chickens. Moreover, influenza A virus (IAV) is highly variable and can spread across species, thereby resulting in a threat to global public health. Therefore, the cross-talk between the host (i.e., chickens) and viruses during infections is critical to understanding viral pathogenesis and antiviral immunity in chicken production. Over the past decade, studies have attempted to depict the cross-talk between the host and virus from different aspects (e.g., microRNA [miRNAs] perspective) and have made progress in this area (Li et al., 2014a; Skalsky and Cullen, 2010).

miRNAs are short noncoding 18- to 25-nucleotide-long RNAs that regulate gene expression at the posttranscriptional level. Substantial evidence

demonstrates that a single miRNA can have extensive and crucial effects on a range of fundamental biological processes, and miRNA dysregulation can result in biological dysfunction and diseases (Bartel, 2004; Ha and Kim, 2014). Pathogen-induced phenotypic changes in hosts are always accompanied by remarkable alterations at the transcriptional level (Jenner and Young, 2005). The miRNA expression profile is profoundly influenced by viral infection and contributes to the repertoire of virus-host interactions. Differential miRNA expression can be attributed to both host antiviral defenses and alterations in cellular environment that are affected by viral factors (Scaria et al., 2007; Skalsky and Cullen, 2010; tenOever, 2013; Harwig et al., 2014; Powdrill et al., 2016; Nejad et al., 2018). Moreover, miRNAs have been reported to be biomarkers of viral infections (Wang et al., 2014) and have roles in viral reactivation from latency (Hicks et al., 2019). Therefore, the identification of deregulated miRNAs in virally infected chickens will provide novel insight into understanding virus-host interaction. In this review, we will summarize recent advances into the critical role of virally influenced poultry and viral miRNAs in the cross-talk between the host and virus to help understand viral pathogenesis and antiviral immunity in the poultry industry. Figure 1 shows the

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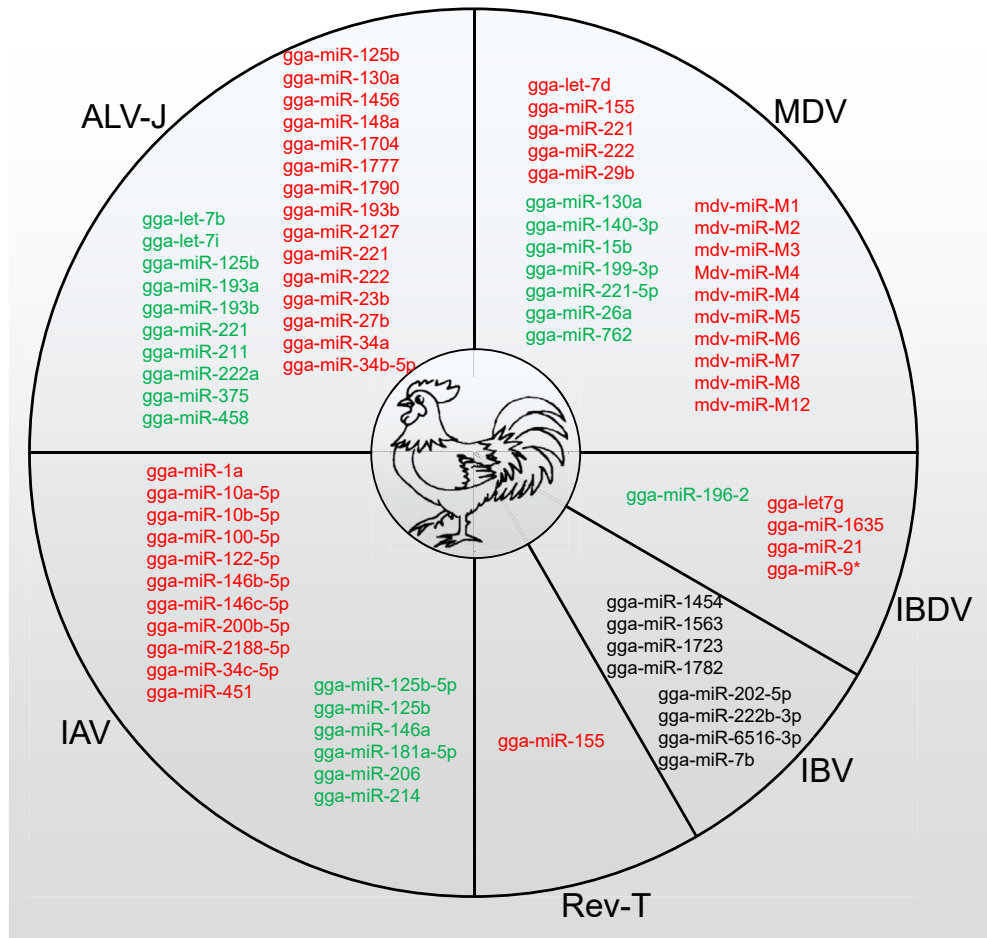


Figure 1. Summary of deregulated miRNAs in viral infected chickens. Red: upregulated microRNAs. Green: downregulated microRNAs. Black: expressed microRNAs. Chicken (*Gallus gallus*) microRNAs started with “gga-miR” while the MDV microRNAs started with “MDV-miR”. Abbreviations: ALV-J, avian leukosis virus subgroup J; IAV, influenza A virus; IBDV, infectious bursal disease virus; IBV, infectious bronchitis virus; MDV, Marek’s disease virus; Rev-T, reticuloendotheliosis virus strain T.

deregulation of miRNAs in chickens and viruses, infected by various viruses including MDV, avian leukosis virus subgroup J (**ALV-J**), IAV, infectious bursal disease virus (**IBDV**), infectious bronchitis virus (**IBV**), or reticuloendotheliosis virus strain T (**Rev-T**). Chicken (*Gallus gallus*) miRNAs started with “gga-miR” while the MDV miRNAs started with “MDV-miR”.

MAREK’S DISEASE VIRUS

MDV is a highly contagious alpha herpesvirus and the causative agent of T-cell lymphoma and Marek’s disease in chickens. The chickens and MDV-encoded miRNAs have been reported to have regulatory roles during MDV oncogenesis (Table 1).

The dysregulation of chicken miRNAs was observed in MDV-infected samples and may play a crucial role in Marek’s disease tumorigenesis. The overexpression of gga-miR-221/-222 decreased the levels of cell cycle regulatory protein p27(Kip1) in the MDV-transformed lymphoblastoid cell line MSB-1 (Lambeth et al., 2009). The level of gga-miR-29b and that of gga-miR-155 expression increased and that of gga-miR-762 decreased in MDV-infected chicken splenic tumors when compared with

non-tumorous tissues (Li et al., 2014c). Several miRNAs are also related to the proliferation or migration of MDV-transformed lymphoid cells. It was found that gga-miR-130a targets HOXA3 and MDFIC and inhibits MSB-1 cell proliferation and migration (Han et al., 2016). The dysregulation of gga-miR-199-3p, gga-miR-140-3p, and gga-miR-221-5p was observed during the early tumor transformation phase and demonstrated a suppressive role on cell proliferation (Lian et al., 2015). Moreover, gga-miR-26a was also downregulated in MDV-infected spleens and suppressed the proliferation of MSB-1 cells (Li et al., 2014b). MDV infection affects the miRNA expression levels not only in spleens but also in the skin tissues, such as gga-let-7d, which was upregulated in the skin of MDV-infected chickens (Heidari and Delekta, 2017).

In the MDV-infected chickens, MDV-encoded miRNAs were found to be stably expressed to enable MDV pathogenesis and contribute to MDV-induced transformation and oncogenesis. Mdv-miR-M4, which flanks the Meq oncogene, was highly expressed in MDV-infected cells and MDV-induced tumors compared with noninfected samples and targeted both chicken and viral genes (Burnside et al., 2006; Xu et al., 2008; Yao et al.,

Table 1. miRNAs have been reported to have regulatory roles during MDV infection in chickens.

miRNA	Species	Source	Pattern	Targets	Cell function	Reference
let-7d	Chicken	Skin	Up	-	-	Heidari and Delekta, 2017
miR-130a	Chicken	Spleens	Down	HOXA3, MDFIC	Inhibit MD lymphoma cell proliferation and migration	Han et al., 2016
miR-140-3p	Chicken	Spleens	Down	-	Inhibit MDV-transformed lymphoid cells proliferation; MD lymphoma transformation	Lian et al., 2015
miR-155	Chicken	Cell lines, peripheral blood leukocytes	Up	GPM6B, RREB1, c-Myb, MAP3K7IP2, PU.1, C/EBP	-	Muylkens et al., 2010
miR-155	Chicken	Spleens	Up	-	-	Li, Zhang, Li, Zheng, Zheng and Liu, 2014c
miR-15b	Chicken	Spleens	Down	ATF2	-	Tian et al., 2012
miR-199-3p	Chicken	Spleens	Down	-	Inhibit MDV-transformed lymphoid cells proliferation; MD lymphoma transformation	Lian et al., 2015
miR-221	Chicken	Cell lines	Up	p27(Kip1)	-	Lambeth et al., 2009
miR-221-5p	Chicken	Spleens	Down	-	Inhibit MDV-transformed lymphoid cells proliferation; MD lymphoma transformation	Lian et al., 2015
miR-222	Chicken	Cell lines	Up	p27(Kip1)	-	Lambeth et al., 2009
miR-26a	Chicken	Spleens	Down	NEK6	Suppress MD lymphoma cell proliferation	Li, Lian, Zhang, Qu and Yang, 2014b
miR-29b	Chicken	Spleens	Up	-	-	Li, Zhang, Li, Zheng, Zheng and Liu, 2014c
miR-762	Chicken	Spleens	Down	-	-	Li, Zhang, Li, Zheng, Zheng and Liu, 2014c
miR-12	MDV	Cell lines, kidney or spleen tissues	Up	-	Potential biomarkers for MDV-transformed tumors and lymphoblastoid cell lines.	Xu et al., 2008
miR-4	MDV	Cell lines, kidney or spleen tissues	Up	-	Potential biomarkers for MDV-transformed tumors and lymphoblastoid cell lines.	Xu et al., 2008
miR-8	MDV	Cell lines, kidney or spleen tissues	Up	-	Potential biomarkers for MDV-transformed tumors and lymphoblastoid cell lines.	Xu et al., 2008
miR-M1	MDV	Cell lines, spleens	Up	-	-	Burnside et al., 2006
miR-M12-3p	MDV	Spleens	Up	-	-	Li, Zhang, Li, Zheng, Zheng and Liu, 2014c
miR-M1-5p	MDV	Spleens	Up	-	-	Li, Zhang, Li, Zheng, Zheng and Liu, 2014c
miR-M2	MDV	Cell lines, spleens	Up	-	-	Burnside et al., 2006
miR-M2*/3p	MDV	Spleens	Up	-	-	Morgan et al., 2008
miR-M2-5p	MDV	Spleens	Up	-	-	Li, Zhang, Li, Zheng, Zheng and Liu, 2014c
miR-M3	MDV	Cell lines, spleens	Up	-	-	Burnside et al., 2006
miR-M3-5p	MDV	Cell line	Up	-	-	Yao et al., 2008
miR-M4	MDV	Spleens	Up	-	-	Morgan et al., 2008
miR-M4	MDV	Embryo fibroblast cultures	Up	-	Variants within its seed region were sufficient to inhibit the induction of lymphomas.	Zhao et al., 2011
miR-M4	MDV	Cell lines, spleens	Up	-	-	Burnside et al., 2006
miR-M4	MDV	Spleens	Up	-	-	Burnside and Morgan, 2011
miR-M4-5p	MDV	Cell lines	Up	-	-	Yao et al., 2008
miR-M4-5p	MDV	Spleens	Up	-	-	Li, Zhang, Li, Zheng, Zheng and Liu, 2014c
miR-M4-5P	MDV	Cell lines, peripheral blood	Up	GPM6B, RREB1, c-Myb, MAP3K7IP, PU.1, C/EBP, UL28, UL32	-	Muylkens et al., 2010
miR-M5	MDV	Cell lines, spleens	Up	-	-	Burnside et al., 2006
miR-M5-3p	MDV	Cell lines	Up	-	-	Yao et al., 2008
miR-M6-5p	MDV	Cell lines	Up	-	-	Yao et al., 2008
miR-M7-5p	MDV	Cell lines	Up	-	-	Yao et al., 2008
miR-M8-3p	MDV	Spleens	Up	-	-	Li, Zhang, Li, Zheng, Zheng and Liu, 2014c

“-” Means no targets of the microRNA in the reference.

Abbreviations: MD, Marek's disease; MDV, Marek's disease virus; miRNA, microRNA.

2008; Muylkens et al., 2010; Burnside and Morgan, 2011; Li et al., 2014c). In particular, in the MDV-induced tumors, the level of mdv-miR-M4 was threefold higher in very virulent plus MDV-induced tumors than in less virulent samples (Morgan et al., 2008). Furthermore,

mutations in mdv-miR-M4 were sufficient to inhibit the induction of lymphomas (Zhao et al., 2011). In addition to mdv-miR-4, mdv-miR-M1 to -M8 were also upregulated in the MDV-infected samples, among which miR-1 was mapped downstream of the Meq gene, mdv-

Table 2. miRNAs have been reported to play a regulatory role during ALV-J infection in chickens.

miRNA	Source	Pattern	Targets	Cell function	Reference
let-7b	Liver	Down	-	-	Li et al., 2012
let-7i	Liver	Down	-	-	Li et al., 2012
miR-125b	Liver	Down	-	-	Li et al., 2012
miR-125b	Bone marrow dendritic cells	Up	-	-	Liu et al., 2016
miR-125b	Cell lines, liver	Down	-	-	Wang, Gao, Ji, Qi, Qin, Gao, Wang and Wang, 2013a
miR-130a	Bone marrow dendritic cells	Up	-	-	Liu et al., 2016
miR-1456	Liver	Up	-	-	Li et al., 2012
miR-148a	Bone marrow dendritic cells	Up	-	-	Liu et al., 2016
miR-1704	Liver	Up	-	-	Li et al., 2012
miR-1777	Liver	Up	-	-	Li et al., 2012
miR-1790	Liver	Up	-	-	Li et al., 2012
miR-193a	Cell lines, liver	Down	-	-	Wang, Gao, Ji, Qi, Qin, Gao, Wang and Wang, 2013a
miR-193b	Bone marrow dendritic cells	Up	-	-	Liu et al., 2016
miR-193b	Cell lines, liver	Down	-	-	Wang, Gao, Ji, Qi, Qin, Gao, Wang and Wang, 2013a
miR-211	Bone marrow dendritic cells	Down	-	-	Liu et al., 2016
miR-2127	Liver	Up	-	-	Li et al., 2012
miR-222	Liver	Up	-	-	Li et al., 2012
miR-221	Bone marrow dendritic cells	Down	-	-	Liu et al., 2016
miR-221	Cell line, liver tissue	Up	CDKN1B	Promote cell proliferation and cell cycle progression	Ren et al., 2018
miR-221	Liver	Up	-	-	Li et al., 2012
miR-221	Cell lines, liver	Up	BMF	Promote the proliferation, migration, and growth of cancer cells, and inhibit apoptosis	Dai et al., 2015
miR-221	Cell lines, liver	Up	-	-	Wang, Gao, Ji, Qi, Qin, Gao, Wang and Wang, 2013a
miR-222	Liver, marrow	Up	BMF	Promote the proliferation, migration, and growth of cancer cells, and inhibit apoptosis	Dai et al., 2015
miR-222a	Bone marrow dendritic cells	Down	-	-	Liu et al., 2016
miR-23b	Spleens	Up	IRF1	Promote ALV-J replication	Li et al., 2015a
miR-27b	Bone marrow dendritic cells	Up	-	-	Liu et al., 2016
miR-34a	Bone marrow dendritic cells	Up	-	-	Liu et al., 2016
miR-34b-5p	Spleens	Up	MDA5	Promote ALV-J infected cells proliferation and ALV-J replication	Li et al., 2017
mir-375	Livers	Down	-	-	Li et al., 2012
mir-458	Livers	Down	-	-	Li et al., 2012

Abbreviations: ALV-J, avian leukosis virus subgroup J; BMF, BCL-2 modifying factor; miRNA, microRNA.

miR-M2 to -M5 were all found to be located upstream of the Meq promoter region, and mdv-miR-M6 to -M8 was mapped to the latency-associated transcript region (Burnside et al., 2006; Xu et al., 2008; Yao et al., 2008; Li et al., 2014c). Moreover, the level of mdv-miR-M2*/3p was more than six-fold higher in very virulent plus MDV-induced tumors than in less virulent samples (Morgan et al., 2008). Mdv-miR-12 was also found to be located upstream of Meq and expressed at high levels in the spleen and kidney tumor tissues compared with normal tissues (Xu et al., 2008; Li et al., 2014c).

AVIAN LEUKOSIS VIRUS SUBGROUP J

Avian leukosis viruses are a group of avian retroviruses that can induce neoplastic diseases in chickens. Specially, an infection with ALV-J can result in serious damage and significant economic loss compared with other virus subgroups because of sporadic or widespread infection (Payne et al., 1991; Gao et al., 2012; Payne and Nair, 2012).

Several miRNAs may play a role as tumor-formation relevant genes in chickens. The overexpression of

gga-miR-221 has been observed in cells, liver tissues, or liver tumors of ALV-J-infected chickens compared with noninfected samples; moreover, gga-miR-221 promoted the proliferation, migration, and growth of cancer cells and inhibited apoptosis by targeting CDKN1B and BCL-2 modifying factor (BMF) (Li et al., 2012; Wang et al., 2013a; Dai et al., 2015; Ren et al., 2018). However, in ALV-J-infected bone marrow dendritic cells, gga-miR-221 was downregulated (Liu et al., 2016). A similar expression pattern and function of gga-miR-222 was also reported in ALV-J-infected samples (Li et al., 2012; Dai et al., 2015; Liu et al., 2016). In addition, gga-miR-125b and -193b also displayed opposing expression patterns in infected liver tissues and dendritic cells. Their expression level was decreased in infected liver tissues but increased in bone marrow dendritic cells (Wang et al., 2013a; Liu et al., 2016). Gga-miR-34b-5p promoted the proliferation and migration of ALV-J-infected cells, as well as ALV-J replication by suppressing melanoma differentiation-associated gene 5 signaling pathway (Li et al., 2017). Other miRNAs reported to exhibit significant levels of expression between infected and noninfected samples are listed in Table 2.

Table 3. miRNAs reported to have a regulatory role during IAV infection.

miRNA	Virus	Species	Source	Pattern	Targets	Reference
miR-100-5p	H9N2	Chicken	CEF	Up	-	Peng et al., 2015
miR-10a-5p	H9N2	Chicken	CEF	Up	-	Peng et al., 2015
miR-10b-5p	H9N2	Chicken	CEF	Up	-	Peng et al., 2015
miR-125b-5p	H9N2	Chicken	CEF	Down	-	Peng et al., 2015
miR-146c-5p	H9N2	Chicken	CEF	Up	-	Peng et al., 2015
miR-181a-5p	H9N2	Chicken	CEF	Down	-	Peng et al., 2015
miR-214	H9N2	Chicken	CEF	Down	-	Peng et al., 2015
miR-125b	H5N3	Chicken	Lung, trachea	Down	-	Wang et al., 2009
miR-146a	H5N3	Chicken	Lung, trachea	Down	-	Wang et al., 2009
miR-1a	H5N3	Chicken	Lung, trachea	Up	-	Wang et al., 2009
miR-206	H5N3	Chicken	Lung	down	-	Wang et al., 2012
miR-451	H5N3	Chicken	Lung	Up	-	Wang et al., 2012
mir-133c	H5N1	Chicken	Lung	Expressed	PB1, PB1-F2, and N40	Kumar et al., 2014
mir-146c*	H5N1	Chicken	Lung	Expressed	PB1, PB1-F2, and N40	Kumar et al., 2014
miR-1658*	H5N1	Chicken	Lung	Expressed	NS1	Asaf et al., 2015
miR-1710	H5N1	Chicken	Lung	Expressed	PB1, PB1-F2, and N40	Kumar et al., 2014
miR-2188-5p	H5N1	Chicken	Spleen	Up	-	Li, Zhang, Su, Liu, Guo, Zhang, Lu, Xing, Guan, Li, Sun and Zhao, 2015b
miR-34c-5p	H5N1	Chicken	Spleen	Up	-	Li, Zhang, Su, Liu, Guo, Zhang, Lu, Xing, Guan, Li, Sun and Zhao, 2015b
miR-200b-5p	H5N1	Chicken	Spleen	Up	-	Li, Zhang, Su, Liu, Guo, Zhang, Lu, Xing, Guan, Li, Sun and Zhao, 2015b
miR-122-5p	H5N1	Chicken	Spleen	Up	-	Li, Zhang, Su, Liu, Guo, Zhang, Lu, Xing, Guan, Li, Sun and Zhao, 2015b
miR-146b-5p	H5N1	Chicken	Spleen	Up	-	Li, Zhang, Su, Liu, Guo, Zhang, Lu, Xing, Guan, Li, Sun and Zhao, 2015b
miR-122-5p	H5N1	Duck	Spleen	Down	-	Li, Zhang, Su, Liu, Guo, Zhang, Lu, Xing, Guan, Li, Sun and Zhao, 2015b

Abbreviations: CEF, chicken embryonic fibroblasts; IAV, influenza A virus; miRNA, microRNA.

INFLUENZA A VIRUS

IAVs are negative-sense single-stranded RNA viruses that can cause significant economic losses to the poultry industry and represent a high threat to global public health because of the potential of overcoming the host barrier, which would allow transmission from animals to humans (Rebmann and Zelicoff, 2012). The rapid mutation rate and evolution of IAVs result in the loss of vaccine optimal efficacy (Shao et al., 2017). Therefore, more effective strategies are required to control AIV. Based on the virus surface glycoproteins, hemagglutinin and neuraminidase, IAVs can be divided into 18 hemagglutinin subtypes and 11 neuraminidase subtypes (Hay et al., 2001). Thus, more effective strategies are required to control IAV. Here, we summarize the regulatory roles of miRNAs in chickens during IAV infection, including H5N3, H5N1, and H9N2 (Table 3).

Because H9N2 is the most common influenza virus in Asia, it has caused large economic losses to chicken production. Moreover, H9N2 has been detected in multiple avian species and can infect humans (Peiris et al., 1999; Xu et al., 2007). Using a deep sequencing platform, Peng et al. measured the expression profiles of miRNAs in H9N2-infected and noninfected chicken embryo fibroblasts and found that 48 miRNAs exhibited significantly different levels of expression between the 2 groups; the miRNAs were predicted to target immune response-related genes (Peng et al., 2015). Among these, the miRNAs that presented with a high abundance (top 10) in the chicken fibroblasts are summarized in Table 3.

H5N1 and H5N3 are highly pathogenic subtypes of avian influenza. Kumar et al. (2014) screened the

miRNAs that were expressed in chicken lungs against the H5N1 genome and found that mir-133c, mir-1710, and mir-146c* were predicted to regulate the viral genes PB1, PB1-F2, and N40, while miR-1658* targeted the viral NS1 gene (Kumar et al., 2014; Asaf et al., 2015). Moreover, the miRNA expression pattern in H5N1-infected chickens and ducks diverged substantially, indicating a difference in the miRNA regulatory networks of the 2 species (Li et al., 2015b). For example, miR-122-5p was upregulated in infected chickens and was predicted to target the genes in the B cell receptor signaling pathway, whereas miR-122-5p was downregulated in ducks and predicted to target RASGRP3. In H5N3-infected chicken lungs, miR-1a, miR-206, miR-451, miR-125b, and miR-146a displayed significantly differentially expressed levels compared with the noninfected lungs (Wang et al., 2009; Wang et al., 2012).

OTHER VIRUSES

IBDV, a member of the genus *Avibirnavirus* of the family *Birnaviridae*, is the etiological agent of infectious bursal disease, which is a highly contagious and immunosuppressive disease affecting young chickens (Brandt et al., 2001; Wang et al., 2007). The overexpression of gga-miR-9* was observed in IBDV-infected specific-pathogen-free chickens and significantly promoted IBDV replication by targeting interferon regulatory factor 2 (Ouyang et al., 2015). Similarly, the overexpression of miR-21 in chicken fibroblasts suppressed IBDV replication by downregulating IBDV VP1 expression (Wang et al., 2013b). Based on the genome-wide profiling of

Table 4. miRNAs that have been reported to have a regulatory role during IBDV, IBV, Rev-T, DTMUV, or DEV infection.

miRNA	Virus	Species	Source	Pattern	Targets	Cell function	Reference
let-7g	IBDV	Chicken	Bone marrow dendritic cells	Up	-	-	Lin et al., 2016
miR-1635	IBDV	Chicken	Bone marrow dendritic cells	Up	-	-	Lin et al., 2016
miR-196-2	IBDV	Chicken	Bone marrow dendritic cells	Down	-	-	Lin et al., 2016
miR-21	IBDV	Chicken	Cell lines	Up	VP1	Suppress replication of IBDV	Wang, Ouyang, Pan, Wang, Xia, Bi, Wang and Wang, 2013b
miR-9*	IBDV	Chicken	Cell lines	Up	IRF2	Promote IBDV replication	Ouyang et al., 2015
miR-1454	IBV	Chicken	Kidney	Up/up/down	-	Associate with the virulence of IBV	Yang et al., 2017
miR-7b	IBV	Chicken	Kidney	Up/up/down	-	Associate with the virulence of IBV	Yang et al., 2017
miR-222b-3p	IBV	Chicken	Kidney	Up/up/up	-	Associate with the virulence of IBV	Yang et al., 2017
miR-1563	IBV	Chicken	Kidney	Down/up/up	-	Associate with the virulence of IBV	Yang et al., 2017
miR-1723	IBV	Chicken	Kidney	Down/up/down	-	Associate with the virulence of IBV	Yang et al., 2017
miR-1782	IBV	Chicken	Kidney	Up/down/down	-	Associate with the virulence of IBV	Yang et al., 2017
miR-202-5p	IBV	Chicken	Kidney	Up/up/up	-	Associate with the virulence of IBV	Yang et al., 2017
miR-6516-3p	IBV	Chicken	Kidney	Up/up/up	-	Associate with the virulence of IBV	Yang et al., 2017
miR-155	REV-T	Chicken	Cell lines	Up	JARID2	Promotes cell survival	Bolisetty et al., 2009
miR-155	REV-T	Chicken	Cell lines	Up	-	-	Yao et al., 2017
miR-7	DTMUV	Duck	DEF	Up	-	-	Cui et al., 2018
miR-133a-3p	DTMUV	Duck	DEF	Down	-	-	Cui et al., 2018
miR-222a	DTMUV	Duck	DEF	Up	-	-	Cui et al., 2018
miR-206	DTMUV	Duck	DEF	Down	-	-	Cui et al., 2018
miR-146b-5p	DTMUV	Duck	DEF	Up	-	-	Cui et al., 2018
miR-1662	DTMUV	Duck	DEF	Down	-	-	Cui et al., 2018
miR-155	DTMUV	Duck	DEF	Up	-	-	Cui et al., 2018
miR-1a-3p	DTMUV	Duck	DEF	Down	-	-	Cui et al., 2018
miR-221-3p	DTMUV	Duck	DEF	Up	-	-	Cui et al., 2018
miR-133a-3p	DEV	Duck	DEF	Up	-	-	Wu et al., 2018
let-7a-2-3p	DEV	Duck	DEF	Up	-	-	Wu et al., 2018
miR-148a-5p	DEV	Duck	DEF	Up	-	-	Wu et al., 2018
miR-34c-5p	DEV	Duck	DEF	Up	-	-	Wu et al., 2018
miR-1a-3p	DEV	Duck	DEF	Up	-	-	Wu et al., 2018
miR-20b-3p	DEV	Duck	DEF	Down	-	-	Wu et al., 2018
miR-125-2-3p	DEV	Duck	DEF	Down	-	-	Wu et al., 2018
miR-215-5p	DEV	Duck	DEF	Down	-	-	Wu et al., 2018
miR-2954-5p	DEV	Duck	DEF	Down	-	-	Wu et al., 2018
miR-29b-1-5p	DEV	Duck	DEF	Down	-	-	Wu et al., 2018
miR-D25-5p	DEV	DEV	DEF	Up	-	-	Wu et al., 2018
miR-D2-3p	DEV	DEV	DEF	Up	-	-	Wu et al., 2018
miR-D26-5p	DEV	DEV	DEF	Up	-	-	Wu et al., 2018
miR-D27-5p	DEV	DEV	DEF	Up	-	-	Wu et al., 2018
miR-D28-3p	DEV	DEV	DEF	Up	-	-	Wu et al., 2018
miR-D29-5p	DEV	DEV	DEF	Up	-	-	Wu et al., 2018
miR-D30-3p	DEV	DEV	DEF	Up	-	-	Wu et al., 2018
miR-D31-3p	DEV	DEV	DEF	Up	-	-	Wu et al., 2018

Abbreviations: DEF, duck embryonic fibroblasts; DEV, duck enteritis virus; DTMUV, Duck Tembusu virus; IBDV, infectious bursal disease virus; IBV, infectious bronchitis virus.

IBDV-infected chicken dendritic cells (DCs), Lin et al. identified 3 transcription factor-miRNA networks in IBDV-simulated DCs (CTCF-Let-7 g, CTCF-miR196-2, and CTCF-miR1635), in which let-7g and miR-1635 were upregulated in IBDV-infected samples and miR196-2 was downregulated (Lin et al., 2016).

IBV is a positive-sense RNA virus of the genus *Gammacoronavirus* that has extensive genetic diversity and a high mutation rate. IBV can cause pathological lesions in the respiratory tract, alimentary tract, kidney, oviduct, and gonads and is the pathogenic agent of avian infectious bronchitis (Cavanagh, 2007). To study the regulation of miRNAs in response to various virulent IBV infections, high-throughput sequencing was performed to determine the level of miRNA expression in the kidneys of noninfected chickens and those infected with attenuated IBV, normal virulent IBV, and highly

virulent IBV (Yang et al., 2017). For example, when compared with noninfected groups, the expression of miR-202-5p, miR-222b-3p, and miR-6516-3p was upregulated in all of the 3 virally infected groups; however, miR-7b and miR-1454 were upregulated in the attenuated IBV and normal virulent IBV groups but downregulated in highly virulent IBV.

Rev-T is a highly oncogenic retrovirus that carries the viral oncogene, *v-rel* (Chen et al., 1981). High levels of miR-155 expression was observed in both Rev-T-infected chicken embryo fibroblast cultures and Rev-T-induced B-cell lymphomas and promoted cellular survival and transformation (Bolisetty et al., 2009; Yao et al., 2017).

To date, there are substantially fewer studies on the expression pattern and function of miRNAs in virus-infected ducks. Duck Tembusu virus (DTMUV) is a

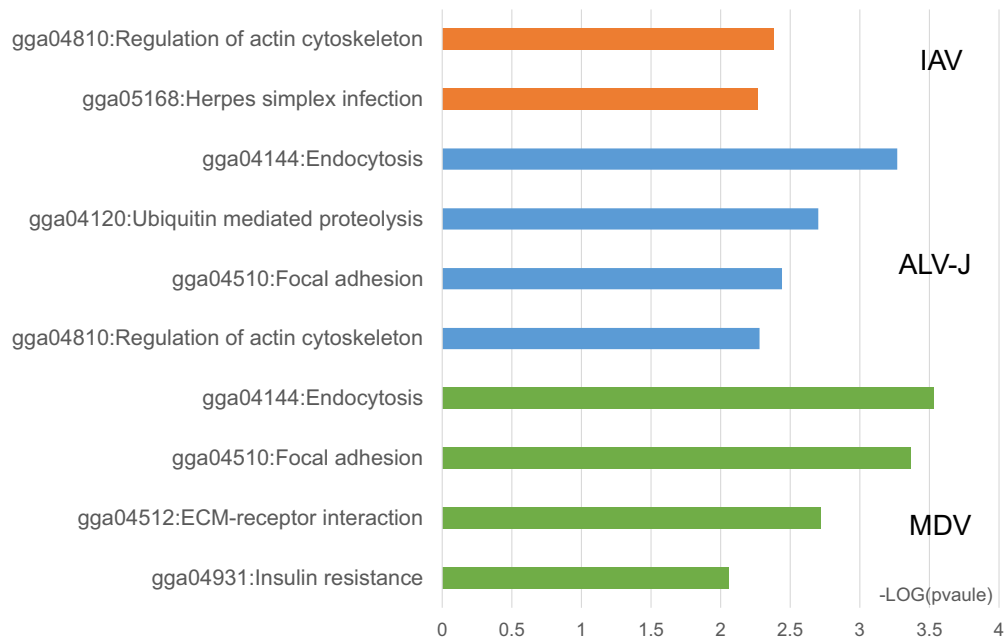


Figure 2. Significant enriched KEGG pathways for the targets of reported dysregulated miRNAs when IAV, ALV-J, and MDV infection occurs. Abbreviations: ALV-J, avian leukosis virus subgroup J; ECM, extracellular matrix; IAV, influenza A virus; KEGG, Kyoto Encyclopedia of Genes and Genomes; MDV, Marek's disease virus.

single-stranded positive RNA virus responsible for substantial economic losses in the duck industry since it was first isolated (Su et al., 2011). Cui et al. analyzed the miRNA expression profiles in DTMUV-infected and uninfected duck embryonic fibroblasts cells using high-throughput sequencing and validated 9 miRNAs that were differentially expressed in response to DTMUV infection (Cui et al., 2018). Duck embryonic fibroblasts infected with virulent duck enteritis virus, a member of the *Herpesviridae* family, displayed a unique pattern of viral miRNAs and a novel set of host miRNAs compared with other strains of duck enteritis virus-attenuated vaccines (Wu et al., 2018). The above deregulated miRNAs are listed in Table 4.

PATHWAYS SIGNIFICANTLY ENRICHED BY THE TARGETS OF DYSREGULATED MIRNAS DURING VIRAL INFECTION

To help understand the mechanisms of how dysregulated miRNAs mediate virus-host interactions, we predicted the targets of the dysregulated miRNAs reported previously during MDV, ALV-J, and IAV infection by miRDB (Liu and Wang, 2019). An enrichment analysis was then subsequently performed by DAVID (Huang da, et al., 2009) to obtain Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways that were significantly enriched by the targets ($P < 0.01$). As shown in Figure 2, there were some common pathways activated under different viral infections. For example, regulation of the actin cytoskeleton was enriched by the targets of the dysregulated miRNAs during IAV or ALV-J infection, whereas focal adhesion and endocytosis were enriched during ALV-J or MDV

infection. However, there are also specific pathways during each type of viral infection (e.g., herpes simplex infection for IAV infection, ubiquitin-mediated proteolysis for ALV-J infection, and insulin resistance and extracellular matrix-receptor interaction pathways for MDV infection). These results indicate that there may be common pathways that are influenced by dysregulated miRNAs during infections with different viruses. There may also be specific pathways activated in response to each viral infection. Thus, different mechanisms may be associated with each infection, which requires further research.

CONCLUSIONS

miRNAs Regulate various biological processes within cells in poultry, including virus infections. Changes in the levels of poultry and viral miRNA expression after viral infection are clearly an important component of the cross-talk between the host and virus. In this review, we provide an extensive overview of the various viruses that infect poultry and involve miRNAs. However, we are just beginning to understand the underlying mechanisms of how the genes targeted by dysregulated miRNAs mediate virus-host interactions. It is important to note the following points: 1) Similar to MDV-infected chickens, some viruses encode their own miRNAs that are expressed during infection, while the host-encoded miRNAs simultaneously regulate viral genes. Moreover, viral miRNAs can also target host genes (Muylkens et al., 2010), which modify the cell environment during infection and add another layer of cross-talk between the host and virus. For future studies, it will be important to elucidate the molecular mechanisms behind these observations; 2) Coinfection of more than one type of

virus in chicken flocks is common and increases the illness severity and threat against poultry health (Sun et al., 2017). The coinfection of viruses in chickens also make the cross-talk between host and virus even more complex. The roles of the miRNA systems in the context of coinfection and pathogenicity require further in-depth research; 3) Recent research has begun to focus on the application of miRNAs to the development of antiviral therapeutics for viruses that threaten human health (e.g., HIV and Ebola) (Janssen et al., 2013; Dunning et al., 2016). However, antiviral therapeutics based on miRNAs in poultry remain limited. Thus, future research tackling these questions are likely to emerge from this exciting area of investigation.

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