Published in final edited form as:
Cytokine. 2008 September ; 43(3): 391–394. doi:10.1016/j.cyto.2008.07.016.

MicroRNAs in the Immune Response

Irene Pedersen and **Michael David**
University of California, San Diego, Division of Biological Sciences, La Jolla, CA

Abstract

MicroRNAs (miRs) were only discovered little more than a decade ago, yet it has become rapidly clear that they are crucial posttranscriptional regulators of gene expression by decreasing the abundance or translational efficiency of mRNAs [1, 2]. While the role of miRs in cell fate decisions linked to proliferation, differentiation and apoptosis was recognized early on, the importance of these non-coding small RNAs on immune system development and response has only recently become evident. In addition to facilitating cell fate decisions of immune cells (e.g. miR-181a and miR-223), miRs also regulate central elements of the adaptive immune response such as antigen presentation (e.g. miR-155) and T-cell receptor signaling (mir-181a). Furthermore, miRs are involved in innate immunity through regulation of Toll-like receptor signaling and cytokine responses (e.g. miR-146). Intriguingly, cellular miRs not only alter immune cell development and function, but are also able to directly affect viral replication. Conversely, virus-encoded miRs shape the host-virus interactions and regulate the viral life cycle. Here we provide a brief overview on the role of cellular and viral miRs in the development and function of the immune system.

MIRs IN IMMUNE SYSTEM DEVELOPMENT

Dicer is a key enzyme in the generation of miRs, and its absence precludes the formation of mature miRs. T cell-specific abrogation of Dicer expression results in significantly reduced T cell numbers, and even though $CD4^+/CD8^+$ T cell lineage commitment appears to be largely unaffected [3, 4], the impaired development of regulatory T cells leads to autoimmune pathology [5]. Deletion of Dicer at the early B cell stage causes an almost complete block at the pro- to pre-B cell transition that coincides with a significant upregulation of the pro-apoptotic protein Bim [6]. This broad ablation of miR expression illustrates the importance of miRs in general in the development and function of the immune system, and tightly coordinated expression of specific miRs has over the last few years been shown to influence myeloid and lymphoid lineage commitments [7, 8]. Importantly, more information is rapidly becoming available on the specific roles of individual miRs in immune system development. (Table 1)

Chen et al. reported that miR-181a is highly expressed in the thymus, and is also detectable in the spleen and bone marrow progenitors and $B220^+$ B cells. Ectopic expression of miR-181a in hematopoietic stem/progenitor cells leads to an increase in B-lymphocytes, with a concomitant decrease in T lymphoid cells, particularly $CD8^+$ T cells [9]. This appears to be a modulatory control rather than a developmental switch, as the increase in B-lineage cells did not completely block the differentiation of other lymphoid and myeloid cell types. The strong expression of miR-181a in the thymus and its enrichment in $CD4^+CD8^+$ cells

suggested a contribution to T cell development. Indeed, miR-181a appears to target Bcl-2, CD69 and the T cell receptor, all of which coordinately mediate positive selection [8, 9]. Furthermore, miR-181a regulates T cell selection by altering their sensitivity to peptide antigens, an effect that is at least partly achieved through the downregulation of multiple phosphatases that act as negative regulators of T cell receptor signaling [10].

miR-150 is induced during B and T cell maturation and is found in mature, resting B- and T-cells, but not in their progenitors. Its presence in splenic B or naïve T cells, but not in pro-B cells or T_{H1} or T_{H2} clones further supports the notion of a developmental role of miR-150, which is further supported by a lack of miR-150 expression in Rag2-deficient spleen and thymus [11]. Interestingly, when ectopically expressed in hematopoietic stem cells, miR-150 significantly blocks pro-B to pre-B stage transition, but has little effect on the formation of $CD4^+$ or $CD8^+$ T cell or myeloid cells [12]. Xiao et al. demonstrated that the expression of the primary predicted target of miR-150, the transcription factor c-Myb which directs multiple steps of lymphocyte development, is indeed controlled by miR-150 *in vivo*, and miR-150 and c-Myb-deficient mice display mostly opposing phenotypes [13]. Conversely, miR-150 transgenic mice show a phenotype similar to c-Myb−/− animals with respect to abnormal B cell development and loss of B1 cells [13].

The *BIC* locus, which represents a common retroviral integration site in chicken, encodes miR-155, a microRNA that has received a lot of attention due to its oncogenic potential and elevated expression in human lymphomas [14–17]. The identification of a viral orthologue of miR-155 in Kaposi's-sarcoma-associated herpes virus (KSHV) raises the possibility that this viral miR may contribute to the induction of KSHV-positive B-cell tumors [18]. MiR-155 expression is up-regulated in activated B and T cells [19], in germinal center B cells and in activated monocytes [20]. Abrogated expression of miR-155 leads to defects in germinal center formation and Ig class switching [21, 22] as well as a skewing towards the T_{H2} lineage [22, 23], while forced B-cell specific expression causes lymphoblastic leukemia/high-grade lymphoma [24]. The activation-Induced Cytidine Deaminase (AID) has been identified as an important target for regulation by miR-155 [25, 26].

Similar to miR-155, the miR-17~92 locus encoding miRs-17, 18a, 19a, 20a, 19b-1 and 92-1 harbors oncogenic potential, and miR-17~92 transcripts are elevated in B cell lymphomas [27]. Absence of miR-17~92 leads to increased levels of Bim and inhibits B cell development at the pro-B to pre-B transition [28]. Conversely, ectopic expression of miR-17~92 in lymphocytes leads to loss of Bim and PTEN, and causes lymphoproliferative disease and autoimmunity [29]. This overexpression of miR-17–92 also yields increased numbers of $CD4^+$ T cells in the periphery, and activated $CD4^+$ T cells produced more IFNγ and IL-10, but not IL-4, correlating with higher serum levels of IgG2a and IgG3, but not IgG1 [29].

Many additional miRs have now been implicated in myeloid or lymphoid differentiation, albeit their specific functions are less well understood. The loci for miR-142, miR-15, and miR-16 are at sites of translocation breakpoints or deletions linked to human leukemias [9]. Ectopic expression of miR-142s was found to have no significant effect on B lymphocytes, but substantially alters lineage differentiation within the T cell compartment [9]. MiR-669c and miR-297 are specifically upregulated in $CD4^+$ T cells, whereas miR-15b, miR-24, miR-27a and miR-150 were more prominent in $CD8^+$ cells, suggesting that these miRs function in the development or function of these respective cells [8]. MiR-223, which is mostly confined to the myeloid cell lineage and promotes granulocyte differentiation, is part of a regulatory loop that involves C/EBP and NFI-A [9, 30].

MIRs IN THE IMMUNE RESPONSE

Expression of several miRNAs (e.g. miR-21, miR-22, miR-24, miR-103, miR-155, miR-204) is elevated in activated T cells *in-vitro*, while miR-16, miR-26, miR-30, miR-150 and miR-181 were suppressed after CD3 stimulation [5]. While the exact function of most of these miRs in T cell activation remains elusive, a recent study by Li et al. [10] elucidated the process of miR-181 modulation of T cell selection in the thymus. MiR-181a affects T cell responses to antigens by altering the strength and threshold of TCR signaling through coordinated downregulation of several phosphatases that act as negative regulators of T cell activation in response to antigens [10]. This inflection of TCR signaling by miR-181 not only defines both positive and negative selection during thymic development, but suggests that miR-181 is also likely to exert control over T cell mediated adaptive immune responses.

The role of miR-150, which is similarly suppressed upon T cell activation and is also subject to down-regulation by Foxp3, a transcription factor characteristic for regulatory T cells [5], in T cell function remains unclear. In B lymphocytes, where miR-150 expression is down-regulated following activation by IgM-specific antibodies, CpG-containing DNA or lipopolysaccharide (LPS), more information is available on its developmental contributions compared to its role in B cell activation upon antigen encounter [13].

MiR-155 deficient mice are characterized by impaired germinal center formation, Ig class switching (likely due to aberrant AID expression) and lower levels of IgM [21, 22, 25, 26]. Reduced IL-2 and IFNγ production, a tendency to differentiate towards the Th2 lineage and a failure to mount an adequate immune protection upon vaccination also substantiate a vital role for miR-155 in T cell responses as well [23].

Interestingly, miR-155 together with miR-146 and miR-132 is also crucially involved in innate immunity by regulating the acute inflammatory response after pathogen recognition by Toll-like receptors (TLRs) on monocytes or macrophages [20, 31]. Inducible expression of miR-155 was observed during both bacterial and viral infections, as well as after exposure of cells to proinflammatory cytokines such as IFNβ, IFNγ or TNFα. In contrast, miR-146 increases were mostly restricted to induction by bacterially derived ligands or IL-1 and TNFα [20, 31]. Both miRs appear to function as components of negative feedback loops attenuating TLR signaling pathways, whereby miR-146 limits IRAK1 and TRAF6 expression [20], and FADD, RIP and IKKε are suppressed by miR-155 [32]. Conversely, miR-125b which represses TNFα, is downregulated by LPS, thus allowing for TNFα production to occur after TLR ligation, while ensuring the suppression of this proinflammatory cytokine under non-infectious conditions [32].

Until a few years ago, no evidence existed to support a role for cellular miRs in the antiviral immune response. On the contrary, Jopling et al. demonstrated that the predominantly hepatocyte-expressed miR-122 was a prerequisite for Hepatitis C virus (HCV) replication, likely mediated by a direct interaction between miR-122 and the 5′ noncoding region of the viral genome [33]. These findings were further corroborated by the observation that disruption of the RNAi silencing pathway inhibits HCV replication [34]. More recent studies, however, support the notion that cellular miRs do indeed contribute to the innate immune response against viral infection. MiR-32 is able to restrict the accumulation of primate foamy virus type 1 (PFV-1) in human cells. Furthermore, PFV-1 also encodes a protein, Tas, that suppresses microRNA-directed functions, suggesting that the RNAi response is detrimental to the viral life cycle [35]. Mice carrying a variant Dicer allele display hypersensitivity towards vesicular stomatitis virus (VSV) infection. This effect be traced back to a loss of miR-24 and miR-93, which inhibit expression of viral proteins, and mutant VSV lacking the target sites for miR-24 and miR-93 replicates more efficiently in

wild-type, but not in Dicer$^{-/-}$ animals [36]. Similarly, Triboulet et al. reported that HIV-1 replication in T-cells is enhanced under circumstances of reduced Dicer or Drosha expression, and that HIV-1 in turn promotes its own replication through increased histone acetyl-transferase (PCAF) expression via attenuated transcription of the miR-17~92 cluster [37]. Intriguingly, HIV-1 Tat appears to inhibit Dicer function in an RNA-dependent manner, thus supporting the notion of a miR-based antiviral status [38, 39]. Finally, we recently reported the upregulation of several cellular miRs in response to treatment of hepatocytes with the antiviral cytokine IFNβ, with a concomitant down-regulation of miR-122. Several of these interferon-induced miRs (miR-196, miR-296, miR-351, miR-431, miR-448) displayed seed sequence matches within the HCV genome and, when ectopically expressed, reduced HCV replication. Mutation of the predicted target sites of miR-196 and miR-448 in the HCV genome obliterated the inhibitory effect of these miRs on HCV replication [40].

VIRAL MIRS AND IMMUNE SUBVERSION

Increased understanding of Immune modulation via RNAi over the last few years revealed that not only cellular, but also virus-derived miRs are an integral component of the virus-host interaction [41, 42]. (Table 2) It is not surprising to find that viruses have evolved to utilize miRs to their advantage, as they require comparatively little coding space in the viral genome, while at the same time remaining ‘undetected’ due to their lack of antigenicity. Interestingly, viral miRs seem to be unique to DNA viruses, with the potential, but still controversial exception of HIV-1 [38, 41, 43, 44]. Two basic mechanisms have emerged by which virally-encoded miRs can alter the host-pathogen interplay.

In the first scenario, viral miRs suppress the innate immune response by targeting cellular transcripts. It had been suggested that the herpes simplex virus-1 (HSV-1) LAT transcript encodes a miR that inhibits apoptosis and promotes latency by targeting TGFβ and SMAD3 [45]. While this article was subsequently retracted, a new study confirmed that the LAT transcript indeed functions as a miR precursor, albeit encoding distinctive miRs with different target specificity [46]. The MHC class I-related chain B (MICB) transcript, which encodes a ligand for the NK cell receptor NKG2D, was recently identified as the target of a miR encoded in the UL112 region of human cytomegalovirus [47]. KSHV was reported to harbor at least 12 miRs [48, 49] cooperatively targeting osteopontin and thrombospondin-1 (THBS1). THBS1 activates TGFβ, and its suppression by KSHV-encoded miRs might account for the reduced TGFβ activity correlated with KSHV pathogenesis [50].

Alternatively, viruses use their miRs to alter host cell responses and/or promote their life cycle by targeting viral transcripts. This seems to be a predominant mechanism in the establishment of viral latency, as demonstrated in the cases of Epstein-Barr virus (EBV) or KSHV. In the former, two miR clusters, BART and BHRF1, promote viral latency in B cell and epithelial cells, respectively [51–53]. Similarly, miRs expressed during late simian virus 40 (SV40) infection target early viral mRNAs such as the T antigen, thereby reducing the susceptibility of infected cells to killing by cytotoxic T cells [54]. Notably, even the apparent ‘antiviral’ properties of cellular miRs might not always be detrimental to viral survival, as illustrated by the contributions of miR-28, miR-125b, miR-150, miR-223 and miR-382 to the establishment of HIV-1 latency in CD4^{+} T cells [55]. Comprehensive and more detailed summaries of the roles of cellular and viral miRs in viral infection and immunity have been published recently [56, 57].

CONCLUSION

The discovery of miRs as posttranscriptional regulators has added yet another layer of complexity to the mechanisms that govern the development and function of the immune system. The elucidation of the roles of 500+ cellular miRs and the still increasing number of virally encoded miRs with complex combinatorial and sometimes redundant functions will pose enormous new challenges to researchers, but might also bestow novel opportunities for therapeutic intervention.

References

1. Maroney PA, Yu Y, Nilsen TW. MicroRNAs, mRNAs, and translation. Cold Spring Harb Symp Quant Biol. 2006; 71:531–5. [PubMed: 17381336]
2. Nilsen TW. Mechanisms of microRNA-mediated gene regulation in animal cells. Trends Genet. 2007; 23:243–9. [PubMed: 17368621]
3. Cobb BS, Nesterova TB, Thompson E, Hertweck A, O'Connor E, Godwin J, Wilson CB, Brockdorff N, Fisher AG, Smale ST, Merkenschlager M. T cell lineage choice and differentiation in the absence of the RNase III enzyme Dicer. J Exp Med. 2005; 201:1367–73. [PubMed: 15867090]
4. Muljo SA, Ansel KM, Kanellopoulou C, Livingston DM, Rao A, Rajewsky K. Aberrant T cell differentiation in the absence of Dicer. J Exp Med. 2005; 202:261–9. [PubMed: 16009718]
5. Cobb BS, Hertweck A, Smith J, O'Connor E, Graf D, Cook T, Smale ST, Sakaguchi S, Livesey FJ, Fisher AG, Merkenschlager M. A role for Dicer in immune regulation. J Exp Med. 2006; 203:2519–27. [PubMed: 17060477]
6. Koralov SB, Muljo SA, Galler GR, Krek A, Chakraborty T, Kanellopoulou C, Jensen K, Cobb BS, Merkenschlager M, Rajewsky N, Rajewsky K. Dicer ablation affects antibody diversity and cell survival in the B lymphocyte lineage. Cell. 2008; 132:860–74. [PubMed: 18329371]
7. Chen CZ, Lodish HF. MicroRNAs as regulators of mammalian hematopoiesis. Semin Immunol. 2005; 17:155–65. [PubMed: 15737576]
8. Neilson JR, Zheng GX, Burge CB, Sharp PA. Dynamic regulation of miRNA expression in ordered stages of cellular development. Genes Dev. 2007; 21:578–89. [PubMed: 17344418]
9. Chen CZ, Li L, Lodish HF, Bartel DP. MicroRNAs modulate hematopoietic lineage differentiation. Science. 2004; 303:83–6. [PubMed: 14657504]
10. Li QJ, Chau J, Ebert PJ, Sylvester G, Min H, Liu G, Braich R, Manoharan M, Soutschek J, Skare P, Klein LO, Davis MM, Chen CZ. miR-181a is an intrinsic modulator of T cell sensitivity and selection. Cell. 2007; 129:147–61. [PubMed: 17382377]
11. Monticelli S, Ansel KM, Xiao C, Socci ND, Krichevsky AM, Thai TH, Rajewsky N, Marks DS, Sander C, Rajewsky K, Rao A, Kosik KS. MicroRNA profiling of the murine hematopoietic system. Genome Biol. 2005; 6:R71. [PubMed: 16086853]
12. Zhou B, Wang S, Mayr C, Bartel DP, Lodish HF. miR-150, a microRNA expressed in mature B and T cells, blocks early B cell development when expressed prematurely. Proc Natl Acad Sci U S A. 2007; 104:7080–5. [PubMed: 17438277]
13. Xiao C, Calado DP, Galler G, Thai TH, Patterson HC, Wang J, Rajewsky N, Bender TP, Rajewsky K. MiR-150 controls B cell differentiation by targeting the transcription factor c-Myb. Cell. 2007; 131:146–59. [PubMed: 17923094]
14. O'Connell RM, Rao DS, Chaudhuri AA, Boldin MP, Taganov KD, Nicoll J, Paquette RL, Baltimore D. Sustained expression of microRNA-155 in hematopoietic stem cells causes a myeloproliferative disorder. J Exp Med. 2008; 205:585–94. [PubMed: 18299402]
15. Tam W, Dahlberg JE. miR-155/BIC as an oncogenic microRNA. Genes Chromosomes Cancer. 2006; 45:211–2. [PubMed: 16252262]
16. Eis PS, Tam W, Sun L, Chadburn A, Li Z, Gomez MF, Lund E, Dahlberg JE. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. Proc Natl Acad Sci U S A. 2005; 102:3627–32. [PubMed: 15738415]

17. Kluiver J, Poppema S, de Jong D, Blokzijl T, Harms G, Jacobs S, Kroesen BJ, van den Berg A. BIC and miR-155 are highly expressed in Hodgkin, primary mediastinal and diffuse large B cell lymphomas. J Pathol. 2005; 207:243–9. [PubMed: 16041695]

18. Gottwein E, Mukherjee N, Sachse C, Frenzel C, Majoros WH, Chi JT, Braich R, Manoharan M, Soutschek J, Ohler U, Cullen BR. A viral microRNA functions as an orthologue of cellular miR-155. Nature. 2007; 450:1096–9. [PubMed: 18075594]

19. Tam W. Identification and characterization of human BIC, a gene on chromosome 21 that encodes a noncoding RNA. Gene. 2001; 274:157–67. [PubMed: 11675008]

20. Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci U S A. 2006; 103:12481–6. [PubMed: 16885212]

21. Vigorito E, Perks KL, Abreu-Goodger C, Bunting S, Xiang Z, Kohlhaas S, Das PP, Miska EA, Rodriguez A, Bradley A, Smith KG, Rada C, Enright AJ, Toellner KM, Maclennan IC, Turner M. microRNA-155 regulates the generation of immunoglobulin class-switched plasma cells. Immunity. 2007; 27:847–59. [PubMed: 18055230]

22. Thai TH, Calado DP, Casola S, Ansel KM, Xiao C, Xue Y, Murphy A, Frendewey D, Valenzuela D, Kutok JL, Schmidt-Supprian M, Rajewsky N, Yancopoulos G, Rao A, Rajewsky K. Regulation of the germinal center response by microRNA-155. Science. 2007; 316:604–8. [PubMed: 17463289]

23. Rodriguez A, Vigorito E, Clare S, Warren MV, Couttet P, Soond DR, van Dongen S, Grocock RJ, Das PP, Miska EA, Vetrie D, Okkenhaug K, Enright AJ, Dougan G, Turner M, Bradley A. Requirement of bic/microRNA-155 for normal immune function. Science. 2007; 316:608–11. [PubMed: 17463290]

24. Costinean S, Zanesi N, Pekarsky Y, Tili E, Volinia S, Heerema N, Croce CM. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. Proc Natl Acad Sci U S A. 2006; 103:7024–9. [PubMed: 16641092]

25. Dorsett Y, McBride KM, Jankovic M, Gazumyan A, Thai TH, Robbiani DF, Di Virgilio M, San-Martin BR, Heidkamp G, Schwickert TA, Eisenreich T, Rajewsky K, Nussenzweig MC. MicroRNA-155 suppresses activation-induced cytidine deaminase-mediated Myc-Igh translocation. Immunity. 2008; 28:630–8. [PubMed: 18455451]

26. Teng G, Hakimpour P, Landgraf P, Rice A, Tuschl T, Casellas R, Papavasiliou FN. MicroRNA-155 is a negative regulator of activation-induced cytidine deaminase. Immunity. 2008; 28:621–9. [PubMed: 18450484]

27. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, Powers S, Cordon-Cardo C, Lowe SW, Hannon GJ, Hammond SM. A microRNA polycistron as a potential human oncogene. Nature. 2005; 435:828–33. [PubMed: 15944707]

28. Ventura A, Young AG, Winslow MM, Lintault L, Meissner A, Erkeland SJ, Newman J, Bronson RT, Crowley D, Stone JR, Jaenisch R, Sharp PA, Jacks T. Targeted deletion reveals essential and overlapping functions of the miR-17 through 92 family of miRNA clusters. Cell. 2008; 132:875–86. [PubMed: 18329372]

29. Xiao C, Srinivasan L, Calado DP, Patterson HC, Zhang B, Wang J, Henderson JM, Kutok JL, Rajewsky K. Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. Nat Immunol. 2008; 9:405–14. [PubMed: 18327259]

30. Fazi F, Rosa A, Fatica A, Gelmetti V, De Marchis ML, Nervi C, Bozzoni I. A minicircuitry comprised of microRNA-223 and transcription factors NFI-A and C/EBPalpha regulates human granulopoiesis. Cell. 2005; 123:819–31. [PubMed: 16325577]

31. O'Connell RM, Taganov KD, Boldin MP, Cheng G, Baltimore D. MicroRNA-155 is induced during the macrophage inflammatory response. Proc Natl Acad Sci U S A. 2007; 104:1604–9. [PubMed: 17242365]

32. Tili E, Michaille JJ, Cimino A, Costinean S, Dumitru CD, Adair B, Fabbri M, Alder H, Liu CG, Calin GA, Croce CM. Modulation of miR-155 and miR-125b levels following lipopolysaccharide/TNF-alpha stimulation and their possible roles in regulating the response to endotoxin shock. J Immunol. 2007; 179:5082–9. [PubMed: 17911593]

33. Jopling CL, Yi M, Lancaster AM, Lemon SM, Sarnow P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. Science. 2005; 309:1577–81. [PubMed: 16141076]
34. Randall G, Panis M, Cooper JD, Tellinghuisen TL, Sukhodolets KE, Pfeffer S, Landthaler M, Landgraf P, Kan S, Lindenbach BD, Chien M, Weir DB, Russo JJ, Ju J, Brownstein MJ, Sheridan R, Sander C, Zavolan M, Tuschl T, Rice CM. Cellular cofactors affecting hepatitis C virus infection and replication. Proc Natl Acad Sci U S A. 2007; 104:12884–9. [PubMed: 17616579]
35. Lecellier CH, Dunoyer P, Arar K, Lehmann-Che J, Eyquem S, Himber C, Saib A, Voinnet O. A cellular microRNA mediates antiviral defense in human cells. Science. 2005; 308:557–60. [PubMed: 15845854]
36. Otsuka M, Jing Q, Georgel P, New L, Chen J, Mols J, Kang YJ, Jiang Z, Du X, Cook R, Das SC, Pattnaik AK, Beutler B, Han J. Hypersusceptibility to vesicular stomatitis virus infection in Dicer1-deficient mice is due to impaired miR24 and miR93 expression. Immunity. 2007; 27:123–34. [PubMed: 17613256]
37. Triboulet R, Mari B, Lin YL, Chable-Bessia C, Bennasser Y, Lebrigand K, Cardinaud B, Maurin T, Barbry P, Baillat V, Reynes J, Corbeau P, Jeang KT, Benkirane M. Suppression of microRNA-silencing pathway by HIV-1 during virus replication. Science. 2007; 315:1579–82. [PubMed: 17322031]
38. Bennasser Y, Le SY, Benkirane M, Jeang KT. Evidence that HIV-1 encodes an siRNA and a suppressor of RNA silencing. Immunity. 2005; 22:607–19. [PubMed: 15894278]
39. Gatignol A, Laine S, Clerzius G. Dual role of TRBP in HIV replication and RNA interference: viral diversion of a cellular pathway or evasion from antiviral immunity? Retrovirology. 2005; 2:65. [PubMed: 16253139]
40. Pedersen IM, Cheng G, Wieland S, Volinia S, Croce CM, Chisari FV, David M. Interferon modulation of cellular microRNAs as an antiviral mechanism. Nature. 2007; 449:919–22. [PubMed: 17943132]
41. Pfeffer S, Zavolan M, Grasser FA, Chien M, Russo JJ, Ju J, John B, Enright AJ, Marks D, Sander C, Tuschl T. Identification of virus-encoded microRNAs. Science. 2004; 304:734–6. [PubMed: 15118162]
42. Pfeffer S, Sewer A, Lagos-Quintana M, Sheridan R, Sander C, Grasser FA, van Dyk LF, Ho CK, Shuman S, Chien M, Russo JJ, Ju J, Randall G, Lindenbach BD, Rice CM, Simon V, Ho DD, Zavolan M, Tuschl T. Identification of microRNAs of the herpesvirus family. Nat Methods. 2005; 2:269–76. [PubMed: 15782219]
43. Omoto S, Ito M, Tsutsumi Y, Ichikawa Y, Okuyama H, Brisibe EA, Saksena NK, Fujii YR. HIV-1 nef suppression by virally encoded microRNA. Retrovirology. 2004; 1:44. [PubMed: 15601474]
44. Ouellet DL, Plante I, Landry P, Barat C, Janelle ME, Flamand L, Tremblay MJ, Provost P. Identification of functional microRNAs released through asymmetrical processing of HIV-1 TAR element. Nucleic Acids Res. 2008; 36:2353–65. [PubMed: 18299284]
45. Gupta A, Gartner JJ, Sethupathy P, Hatzigeorgiou AG, Fraser NW. Anti-apoptotic function of a microRNA encoded by the HSV-1 latency-associated transcript. Nature. 2006; 442:82–5. [PubMed: 16738545]
46. Umbach JL, Kramer MF, Jurak I, Karnowski HW, Coen DM, Cullen BR. MicroRNAs expressed by herpes simplex virus 1 during latent infection regulate viral mRNAs. Nature. 2008
47. Stern-Ginossar N, Elefant N, Zimmermann A, Wolf DG, Saleh N, Biton M, Horwitz E, Prokocimer Z, Prichard M, Hahn G, Goldman-Wohl D, Greenfield C, Yagel S, Hengel H, Altuvia Y, Margalit H, Mandelboim O. Host immune system gene targeting by a viral miRNA. Science. 2007; 317:376–81. [PubMed: 17641203]
48. Cai X, Cullen BR. Transcriptional origin of Kaposi's sarcoma-associated herpesvirus microRNAs. J Virol. 2006; 80:2234–42. [PubMed: 16474131]
49. Cai X, Lu S, Zhang Z, Gonzalez CM, Damania B, Cullen BR. Kaposi's sarcoma-associated herpesvirus expresses an array of viral microRNAs in latently infected cells. Proc Natl Acad Sci U S A. 2005; 102:5570–5. [PubMed: 15800047]
50. Samols MA, Skalsky RL, Maldonado AM, Riva A, Lopez MC, Baker HV, Renne R. Identification of cellular genes targeted by KSHV-encoded microRNAs. PLoS Pathog. 2007; 3:e65. [PubMed: 17500590]

51. Cai X, Schafer A, Lu S, Bilello JP, Desrosiers RC, Edwards R, Raab-Traub N, Cullen BR. Epstein-Barr virus microRNAs are evolutionarily conserved and differentially expressed. PLoS Pathog. 2006; 2:e23. [PubMed: 16557291]
52. Grundhoff A, Sullivan CS, Ganem D. A combined computational and microarray-based approach identifies novel microRNAs encoded by human gamma-herpesviruses. RNA. 2006; 12:733–50. [PubMed: 16540699]
53. Kim do N, Chae HS, Oh ST, Kang JH, Park CH, Park WS, Takada K, Lee JM, Lee WK, Lee SK. Expression of viral microRNAs in Epstein-Barr virus-associated gastric carcinoma. J Virol. 2007; 81:1033–6. [PubMed: 17079300]
54. Sullivan CS, Grundhoff AT, Tevethia S, Pipas JM, Ganem D. SV40-encoded microRNAs regulate viral gene expression and reduce susceptibility to cytotoxic T cells. Nature. 2005; 435:682–6. [PubMed: 15931223]
55. Huang J, Wang F, Argyris E, Chen K, Liang Z, Tian H, Huang W, Squires K, Verlinghieri G, Zhang H. Cellular microRNAs contribute to HIV-1 latency in resting primary CD4+ T lymphocytes. Nat Med. 2007; 13:1241–7. [PubMed: 17906637]
56. Sonkoly E, Stahle M, Pivarcsi A. MicroRNAs and immunity: novel players in the regulation of normal immune function and inflammation. Semin Cancer Biol. 2008; 18:131–40. [PubMed: 18291670]
57. Gottwein E, Cullen BR. Viral and cellular microRNAs as determinants of viral pathogenesis and immunity. Cell Host Microbe. 2008; 3:375–87. [PubMed: 18541214]

Table 1

Regulation of miRs during lymphocyte development (black= upregulated miRs, red = downregulated miRs)

Lympoid Progenitor	B-lineage			
	Pro-B	Pre-B	Mature B	
			Resting	Activated
	142	24	181a	150
		142	150	
	T-lineage			
	DN	DP	CD4	
			Resting	Activated
			29b	let-7c,d
			92	16
			142-3p	21
			181a	22
			297	24
			350	26
			669c	30b,c
				103
				150
		16		155
		20a		
		29b		181
		92		
		128b		214
		142-5p		
		181a		
		350	CD8	
			Resting	Activated
			15b	let-7f
			24	15b
			27a	16
			29b	21
			92	142-3p
			142-3p	142-5p
			150	150
			181a	669d
			350	

Adapted from [56]

Table 2

Summary of MiRs in human viral pathogens

Virus Family	Virus	Known miRs
Herpes Viruses	HSV-1	miR-H1
	hCMV	miR-UL22a miR-UL36 miR-UL70 miR-UL112 miR-UL148D miR-US4 miR-US5-1 miR-US5-2 miR-US25-1 miR-US25-2 miR-US33
	EBV	miR-BART1 to 20 miR-BHRF1-1 miR-BHRF1-2 miR-BHRF1-3
	KSHV	miR-K12-1 to 12
Adenovirus	hAV	not named

Adapted from [57]